Suspected Cancer:
recognition and referral

NICE Guideline
Appendix F: Evidence review

Developed for NICE by the National Collaborating Centre for Cancer

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This guideline updates and replaces NICE guideline CG27
This Evidence Review updates and replaces that in NICE guideline CG27 (published June 2005).

Evidence has been reviewed on the recognition and management of suspected cancer in children, young people and adults. New evidence which has been included as part of this update is highlighted in peach.
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</table>
## Myeloma

- What is the risk of myeloma in patients presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected myeloma should be done with clinical responsibility retained by primary care?

## Non-Hodgkin’s Lymphoma

- What is the risk of Non-Hodgkin’s lymphoma in patients presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected Non-Hodgkin’s lymphoma cancer should be done with clinical responsibility retained by primary care?

## Hodgkin’s Lymphoma

- What is the risk of Hodgkin’s lymphoma in patients presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected Hodgkin’s lymphoma should be done with clinical responsibility retained by primary care?

## Sarcomas

### Bone Sarcoma

- What is the risk of bone sarcoma in patients presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected bone sarcoma should be done with clinical responsibility retained by primary care?

### Soft Tissue Sarcoma

- What is the risk of soft tissue sarcoma in patients presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected soft tissue sarcoma should be done with clinical responsibility retained by primary care?

## Childhood Cancers

### Neuroblastoma, Retinoblastoma, Wilm’s Tumour

- What is the risk of neuroblastoma, retinoblastoma and Wilm’s tumour in children presenting in primary care with symptom(s)?
- Which investigations of symptoms of suspected neuroblastoma, retinoblastoma and Wilm’s tumour in children should be done with clinical responsibility retained by primary care?

## Non-Site Specific Symptoms

- What is the risk of...
PATIENT INFORMATION

Review question:
What are the information needs of: 1) patients who are referred for suspected cancer and their carers/families, and 2) patients who are being monitored (for suspected cancer) in primary care and their carers/families?

Results

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Study results
No evidence was found pertaining to the information needs of primary care patients who are referred for suspected cancer and their carers/families, or of patients who are being monitored (for suspected cancer) in primary care and their carers/families.

References

Included studies
None

Excluded studies (with reason)
Information leaflet, not study data
Not in PICO which is about information, not communication as such, and about what information patients/carers/families want/need or don’t want/need during referral and monitoring.
PATIENT PARTICIPATION Cancer Care Focus Group at Caen Medical Centre. 2013.
Not in PICO
Why have I been referred urgently to the hospital. 2013.
Information, not study data
Not in PICO
Not in PICO

Not in PICO

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Information, not study data

Not in PICO

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Not in PICO

Blumenthal-Barby, J. S., Cantor, S. B., Russell, H. V., Naik, A. D. & Volk, R. J. (2013) - Decision aids: when 'nudging' patients to make a particular choice is more ethical than balanced, nondirective


Methods underspecified. The only mention of information preferences in the results cannot be evaluated or related to any absolute starting point (information level). Input as not in PICO


Not in PICO


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Guideline


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Breast, 22: 919-925.
Not in PICO
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Protocol
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Greater Midlands cancer Network. Primary Care Audit. 2009.
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Suspected Cancer: Appendix F (June 2015)
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

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Narrative review

Test not in PICO

Narrative review

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Duplicate

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Narrative review

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Narrative review

Narrative review

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Knobf, M. T. (328) Treatment options for early stage breast cancer. [Review] [61 refs]. Medsurg Nursing, 3: 249-257.
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Narrative review

Narrative review

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Suspected Cancer: Appendix F (June 2015)


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Narrative review


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Narrative review


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Not in PICO/Narrative review
Royal College of Physicians . Improving communication between doctors and patients report of a working party of the Royal College of Physicians. 1997. Not in PICO
Not in PICO for patient information, and for S & S topics: Symptoms not linked to specific cancers, only to cancer overall


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


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Not in PICO


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Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO

van, H. M., Ranke, G. M., van Nes, J. G., Stiggelbout, A. M., de Bock, G. H. & van de Velde, C. J. (2011) Patients’ needs and preferences in routine follow-up for early breast cancer; an evaluation of the

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SAFETY-NETTING

Review question:
What safety-netting strategies are effective in primary care for patients being monitored for suspected cancer?

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Suspected Cancer: Appendix F (June 2015)

Study results
No evidence was found pertaining to the effectiveness of any safety-netting strategies in primary care for patients being monitored for suspected cancer.

References

Included studies
None

Excluded studies (with reason)
Pancreatic UK’s Early Diagnosis Summit. 2012.
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   Narrative review/guideline
   Narrative review/guideline
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Not in PICO

Narrative review

Narrative review

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Narrative review

Narrative review/guideline

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Narrative review


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Narrative review

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Marghoob, A. A. (146) Basal and squamous cell carcinomas. What every primary care physician should know. [Review] [20 refs]. Postgraduate Medicine, 102: 139-142.
Narrative review

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Narrative review

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Molassiotis, A., Wilson, B., Brunton, L. & Chandler, C. Mapping patients' experiences from initial change in health to cancer diagnosis: A qualitative exploration of patient and system factors mediating this process. [References]. European Journal of Cancer Care 19[1], 98-109. 2010.
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Narrative review/guideline

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Narrative review

Narrative review/guideline

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Yorkshire Cancer Network . Safety Netting in Primary Care.  2013. Narrative review/guideline
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LUNG AND PLEURAL CANCERS

LUNG CANCER

Review question:
What is the risk of lung cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

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Total References retrieved (after de-duplication): 208

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Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note are that patient sampling was not based on a consecutive or random series of patients in a number of the studies, some of which were also not conducted in a population directly relevant to the current question. Studies employing non-consecutive/random sampling are at high risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data, symptom coding and specification as well as suboptimal reference standard.
Table 1: Lung cancer: Meta-analyses

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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<td>Jones (2007, at 6 months), Hippisley-Cox (2011), Iyen-Omofoman (2013)</td>
<td>Haemoptysis</td>
<td>All patients (N = 14516)</td>
<td>3.51 (1.61-7.5)</td>
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Please note that the data from Hamilton (2005) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the second table below.

Table 2: Lung cancer: Individual positive predictive values from the meta-analyses

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<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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<td>Hippisley-Cox (2011)</td>
<td>Haemoptysis</td>
<td>All patients (N = 7861)</td>
<td>6.4 (5.9-7)</td>
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<td>Iyen-Omofoman (2013)</td>
<td>Haemoptysis</td>
<td>All patients (N = 1843)</td>
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<tr>
<td>Jones (2007, at 6 months),</td>
<td>Haemoptysis</td>
<td>All patients (N =4822)</td>
<td>4.8 (4.2-5.5)</td>
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<td>Study</td>
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<td>Deyo (1988)</td>
<td>Back pain</td>
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<td>Muris (1995)</td>
<td>Non-acute abdominal complaints</td>
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<td>Oudega (2006)</td>
<td>Deep vein thrombosis</td>
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<td>Men 75-84 years at 3 years</td>
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Hamilton (2005) also reports that the PPVs for all the variables reported for this study apart from thrombocytosis were higher for patients aged ≥ 70 years than patients aged 40-69 years. In patients aged ≥ 70 years the PPVs ranged from 0.9-2.2% apart from for haemoptysis and abnormal spirometry (see separate entry).

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<th>Cases</th>
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<td>4.1 (NR)</td>
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Hamilton (2005) also reports that the PPVs for all the variables reported for this study apart from thrombocytosis were higher for patients aged ≥ 70 years than patients aged 40-69 years. In patients aged ≥ 70 years the PPVs ranged from 0.9-2.2% apart from for haemoptysis and abnormal spirometry (see separate entry).

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<th>Time Period</th>
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<th>Cases</th>
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<tr>
<td>Abnormal</td>
<td>Controls: 107/12074</td>
<td>Cases: 528/120731</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>Controls: 130/12074</td>
<td>Cases: 911/120731</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iyen-Omofoman (2013)</th>
<th>Outcome of blood tests 13-24 months prior to diagnosis</th>
<th>Derivation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>No blood test record</td>
<td>Cases: 6136/12074</td>
<td>Controls: 79446/120731</td>
</tr>
<tr>
<td>Test without results</td>
<td>Cases: 5632/12074</td>
<td>Controls: 39255/120731</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Cases: 127/12074</td>
<td>Controls: 752/120731</td>
</tr>
<tr>
<td>Normal</td>
<td>Cases: 179/12074</td>
<td>Controls: 1278/120731</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iyen-Omofoman (2013)</th>
<th>Number of GP consultations 4-12 months prior to diagnosis</th>
<th>Derivation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>Cases: 4316/12074</td>
<td>Controls: 77720/120731</td>
</tr>
<tr>
<td>11-20</td>
<td>Cases: 4373/12074</td>
<td>Controls: 29327/120731</td>
</tr>
<tr>
<td>≥21</td>
<td>Cases: 3385/12074</td>
<td>Controls: 13684/120731</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iyen-Omofoman (2013)</th>
<th>Number of GP consultations 13-24 months prior to diagnosis</th>
<th>Derivation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>Cases: 3491/12074</td>
<td>Controls: 64881/120731</td>
</tr>
<tr>
<td>11-20</td>
<td>Cases: 3492/12074</td>
<td>Controls: 29296/120731</td>
</tr>
<tr>
<td>≥21</td>
<td>Cases: 5091/12074</td>
<td>Controls:</td>
</tr>
</tbody>
</table>

Table 4: Lung cancer: Additional results reported by the individual papers: Pairs of signs/symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Signs/Symptoms</th>
<th>Population</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Haemoptysis + current/ex-smoking</td>
<td>Patients ≥ 40 years</td>
<td>9.7 (8.9-10.7)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + cough</td>
<td>All patients</td>
<td>2 (1.1-3.5)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + cough</td>
<td>All smokers</td>
<td>3.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + fatigue</td>
<td>All patients</td>
<td>3.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + fatigue</td>
<td>All smokers</td>
<td>6.1 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + dyspnoea</td>
<td>All patients</td>
<td>4.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + dyspnoea</td>
<td>All smokers</td>
<td>6.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + chest pain</td>
<td>All patients</td>
<td>5 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + chest pain</td>
<td>All smokers</td>
<td>4.1 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + weight loss</td>
<td>All patients</td>
<td>9.2 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + weight loss</td>
<td>All smokers</td>
<td>*</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + appetite loss</td>
<td>All patients</td>
<td>&gt; 10 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + appetite loss</td>
<td>All smokers</td>
<td>*</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + thrombocytosis</td>
<td>All patients</td>
<td>&gt; 10 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + thrombocytosis</td>
<td>All smokers</td>
<td>NR</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + abnormal spirometry</td>
<td>All patients</td>
<td>&gt; 10 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoptysis + abnormal spirometry</td>
<td>All smokers</td>
<td>*</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + cough</td>
<td>All patients</td>
<td>0.63 (0.5-0.9)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + cough</td>
<td>All smokers</td>
<td>1 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + dyspnoea</td>
<td>All patients</td>
<td>0.89 (0.6-?)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + dyspnoea</td>
<td>All smokers</td>
<td>1.4 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + chest pain</td>
<td>All patients</td>
<td>0.84 (0.5-1.3)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + chest pain</td>
<td>All smokers</td>
<td>1.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + weight loss</td>
<td>All patients</td>
<td>1 (0.6-1.7)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + weight loss</td>
<td>All smokers</td>
<td>2 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + appetite loss</td>
<td>All patients</td>
<td>1.2 (0.7-2.1)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + appetite loss</td>
<td>All smokers</td>
<td>2.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + thrombocytosis</td>
<td>All patients</td>
<td>1.8 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Fatigue + thrombocytosis</td>
<td>All smokers</td>
<td>2.4 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Condition 1 + Condition 2</td>
<td>Group</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------</td>
<td>----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Fatigue + abnormal spirometry</td>
<td>All patients</td>
<td>4 (NR)</td>
<td></td>
</tr>
<tr>
<td>Fatigue + abnormal spirometry</td>
<td>All smokers</td>
<td>&gt;10 (NR)</td>
<td></td>
</tr>
<tr>
<td>Cough + dyspnoea</td>
<td>All patients</td>
<td>0.79 (0.6-1)</td>
<td></td>
</tr>
<tr>
<td>Cough + chest pain</td>
<td>All patients</td>
<td>0.76 (0.6-1)</td>
<td></td>
</tr>
<tr>
<td>Cough + chest pain</td>
<td>All smokers</td>
<td>0.9 (NR)</td>
<td></td>
</tr>
<tr>
<td>Cough + weight loss</td>
<td>All patients</td>
<td>1.8 (1.1-2.9)</td>
<td></td>
</tr>
<tr>
<td>Cough + appetite loss</td>
<td>All patients</td>
<td>1.6 (0.9-2.7)</td>
<td></td>
</tr>
<tr>
<td>Cough + appetite loss</td>
<td>All smokers</td>
<td>2.8 (NR)</td>
<td></td>
</tr>
<tr>
<td>Cough + thrombocytosis</td>
<td>All patients</td>
<td>2 (1.1-3.5)</td>
<td></td>
</tr>
<tr>
<td>Cough + thrombocytosis</td>
<td>All smokers</td>
<td>6.5 (NR)</td>
<td></td>
</tr>
<tr>
<td>Cough + abnormal spirometry</td>
<td>All patients</td>
<td>1.2 (0.6-2.6)</td>
<td></td>
</tr>
<tr>
<td>Cough + abnormal spirometry</td>
<td>All smokers</td>
<td>3.6 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + chest pain</td>
<td>All patients</td>
<td>1.2 (0.9-1.8)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + chest pain</td>
<td>All smokers</td>
<td>2.2 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + weight loss</td>
<td>All patients</td>
<td>2 (1.2-3.8)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + weight loss</td>
<td>All smokers</td>
<td>3.1 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + appetite loss</td>
<td>All patients</td>
<td>2 (1.2-3.8)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + appetite loss</td>
<td>All smokers</td>
<td>5.5 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + thrombocytosis</td>
<td>All patients</td>
<td>2 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + thrombocytosis</td>
<td>All smokers</td>
<td>2.4 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + abnormal spirometry</td>
<td>All patients</td>
<td>2.3 (NR)</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea + abnormal spirometry</td>
<td>All smokers</td>
<td>&gt;10 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + weight loss</td>
<td>All patients</td>
<td>1.8 (1-3.4)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + weight loss</td>
<td>All smokers</td>
<td>4.4 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + appetite loss</td>
<td>All patients</td>
<td>1.8 (0.9-3.9)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + appetite loss</td>
<td>All smokers</td>
<td>7.6 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + thrombocytosis</td>
<td>All patients</td>
<td>2 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + thrombocytosis</td>
<td>All smokers</td>
<td>&gt;10 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + abnormal spirometry</td>
<td>All patients</td>
<td>1.4 (NR)</td>
<td></td>
</tr>
<tr>
<td>Chest pain + abnormal spirometry</td>
<td>All smokers</td>
<td>&gt;10 (NR)</td>
<td></td>
</tr>
<tr>
<td>Weight loss + appetite</td>
<td>All patients</td>
<td>2.3 (1.2-4.4)</td>
<td></td>
</tr>
</tbody>
</table>
Hamilton (2005) | Weight loss + appetite loss | All smokers | 5 (NR) |
---|---|---|---|
Hamilton (2005) | Weight loss + thrombocytosis | All patients | 6.1 (NR) |
Hamilton (2005) | Weight loss + thrombocytosis | All smokers | >10 (NR) |
Hamilton (2005) | Weight loss + abnormal spirometry | All patients | 1.5 (NR) |
Hamilton (2005) | Weight loss + abnormal spirometry | All smokers | >10 (NR) |
Hamilton (2005) | Appetite loss + thrombocytosis | All patients | 0.9 (NR) |
Hamilton (2005) | Appetite loss + thrombocytosis | All smokers | * |
Hamilton (2005) | Appetite loss + abnormal spirometry | All patients | 2.7 (NR) |
Hamilton (2005) | Appetite loss + abnormal spirometry | All smokers | * |
Hamilton (2005) | Thrombocytosis + abnormal spirometry | All patients | 3.6 (NR) |
Hamilton (2005) | Thrombocytosis + abnormal spirometry | All smokers | NR |

TP = true positives, FP = false positives, NR = Not reported. * “The original study was not able to calculate figures for these boxes, but they are almost certainly worthy of a red shade [2 week wait referral]”, * effectively means >2%. Please note the calculations of the positive predictive values differ between the studies with Hippisley-Cox (2011) using (TP)/(TP+FP) and Hamilton (2005) using Bayesian statistics due to the case-control design of this study.

**Evidence statement(s):**

Haemoptysis (4 studies, N = 15998) presenting in a primary care setting is associated with overall positive predictive values of 2.4-17% for lung cancer, which tended to increase with age in men and women (1 study, N = 4822). The studies were associated with 0-1 bias or applicability concern (see also Tables 1-3).

Single symptoms other than haemoptysis presenting in a primary care setting is associated with overall positive predictive values from 0.05% (for back pain) to 1.6% (for abnormal spirometry and thrombocytosis) for for lung cancer (6 studies, N = 1833698), and with positive predictive values from 0.9% (for cough) to 4.2% (for thrombocytosis) for smokers for lung cancer (1 study, N = 1482). The studies were each associated with 1-3 bias or applicability concern (see also Table 3).

Two symptoms presenting in combination in a primary care setting were associated with overall positive predictive values from 0.63% (for fatigue and cough) to > 10% (for haemoptysis with appetite loss, abnormal spirometry or thrombocytosis) for lung cancer (2 studies, N = 6030), and with positive predictive values from 0.9% (for chest pain and cough) to > 10% (for abnormal spirometry with fatigue, dyspnoea, chest pain or loss of weight, and for thrombocytosis with chest pain or loss of weight) for smokers for lung cancer (1 study, N = 1482). The studies were each associated with 1 bias concern (see also Table 4).
### Evidence tables

**Deyo (1988)**

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive? patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td><strong>Unclear</strong></td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td><strong>Yes (probably)</strong></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Unclear risk</strong></td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). |
| **Inclusion criteria:** Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint. |
| **Exclusion criteria:** Neck pain. |
| **Clinical setting:** Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million. |

| Are there concerns that the included patients and setting do not match the review question? | High concern |

#### INDEX TEST

**A. Risk of bias**

| Index test | Back pain; not further specified. |
| **Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

**A. risk of bias**

<p>| Reference standard(s) | The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility. |
| <strong>Is the reference standard likely to correctly classify the</strong> | <strong>Unclear</strong> |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All the patients are accounted for in the results.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>NOTES</td>
<td>It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder; 1)</td>
</tr>
</tbody>
</table>

**Hallissey (1990)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Propective consecutive patient series from a group of 10 general practices in England.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 2585 aged &gt; 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: None listed.</td>
</tr>
<tr>
<td></td>
<td>Clinical setting: Primary care, England.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>
### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia of any degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 4 weeks and follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>2659 patients were seen and 2585 attended for investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

### Hamilton (2005)

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### For diagnostic case-control studies:

**Attempts were made within the design or analysis to balance the comparison groups for potential confounders?**

Yes

**For diagnostic case-control studies:**

The groups were comparable at baseline, including all major confounding and prognostic factors?

Yes

### Could the selection of patients have introduced bias?

High risk

### B. Concerns regarding applicability

#### Patient characteristics and setting

| Cases: | N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34. |

**Inclusion criteria:**

Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register.

Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case.

**Exclusion criteria:**

Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis.

**Clinical setting:** Primary care, UK.

#### Are there concerns that the included patients and setting do not match the review question?

Low concern

### INDEX TEST

**A. Risk of bias**

**Index test**

Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**For diagnostic case-control studies:**

Investigators were kept 'blind' to other important confounding and prognostic factors?

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern

### REFERENCE STANDARD

**A. Risk of bias**

**Reference**

Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter...
### Hospital or practice notes.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Flow and Timing

#### Flow and timing

All the patients are accounted for.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Notes

Hippisley-Cox (2011)

**Patient Selection**

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td></td>
</tr>
<tr>
<td>Prospective patient series using patients in the QResearch database</td>
<td></td>
</tr>
<tr>
<td>(version 30).</td>
<td></td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

A total of 1267151 patients were identified from 189 practices (632522 males, 634629 females), mean (SD) age = 49.6 (14.8) years, mean (SD) Townsend score = -0.1 (3.6).

Current symptoms and symptoms in the preceding year:

- Current haemoptysis (N = 8010), current appetite loss (N = 6303), current weight loss (N = 17355), cough in the last year (N = 30298), dyspnoea in the last year (N = 5887), tiredness in the last year (N = 12854), hoarseness (N = 966), haemoglobin recoded in the last year (N = 189945), haemoglobin < 11 g/dl in the last year (N = 8010).

Incident cases of lung cancer during the 2-year follow up period: N = 2196.

Inclusion criteria:

All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ 1 year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from
patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with haemoptysis, appetite loss, or weight loss, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of lung cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of lung cancer; that is, symptoms of haemoptysis, loss of appetite, or weight loss.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Lung tract cancer during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes or ICD-10 diagnostic codes.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>The numbers of patients in the validation cohort reported in text/Table 5 do not correspond to those reported in Table 1, both on terms of total numbers of patients (1243329/1342329 versus 1267151) and number of patients with</td>
</tr>
</tbody>
</table>
The missing data does not appear to include any of the cancer cases, but it is unclear what the effect of the missing data is on the PPVs as clearly some of the false positives are missing.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

Iyen-Omofoman (2013)

#### PATIENT SELECTION

##### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Case-control study using The Health Improvement Network (THIN) database, which had data from 446 UK general practices with a total of 8.2 million patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No (for derivation cohort) Yes (for validation cohort)</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

- Attempts were made within the design or analysis to balance the comparison groups for potential confounders?

**For diagnostic case-control studies:**

- The groups were comparable at baseline, including all major confounding and prognostic factors?

**Could the selection of patients have introduced bias?**

- High risk (for derivation cohort)
- Low risk (for validation cohort)

#### B. Concerns regarding applicability

**Patient characteristics and setting**

|---------|--------------------------------------------------------------------------------------------------|

**Inclusion criteria:**

- Cases: All incident cases of lung cancer diagnosed between 1 January 2000 and 28 July 2009 in patients aged ≥ 40 years.
- Controls: Ten randomly selected controls aged ≥ 40 years with ≥ 1 year of active records were matched to each case on general practice.
- Validation cohort: All THIN patients aged > 39 years, free from lung cancer on
29 July 2009, and ≥ 1 year general practice follow up.

Exclusion criteria:
Cases: Patients with < 1 year of active records prior to their first diagnosis of lung cancer.
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Cough, chest/shoulder pain, dyspnoea, weight loss, hoarseness, upper and lower respiratory tract infections, non-specific chest infections, constipation, depressive disorders, and chronic obstructive pulmonary disease (COPD), recorded over the 2-year period before lung cancer diagnosis.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

For diagnostic case-control studies:
Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Yes</th>
</tr>
</thead>
</table>

Could the conduct or interpretation of the index test have introduced bias?

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Lung cancer diagnosis in THIN database</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

Could the reference standard, its conduct, or its interpretation have introduced bias?

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were all patients included in the analysis?</th>
<th>Yes</th>
</tr>
</thead>
</table>

Could the patient flow have introduced bias?

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

### NOTES

Jones (2007)
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of first occurrences in patients with no previous diagnosis of cancer:</td>
<td>Haematuria: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years.</td>
</tr>
<tr>
<td>Patients excluded due to incomplete dates for their first symptom: N = 30.</td>
<td>Sex (of final sample): 6385 males, 4723 females.</td>
</tr>
<tr>
<td>Haemoptysis: N = 4822, mean (SD) age at first symptom = 61.6 (18) years.</td>
<td>Patients excluded due to incomplete dates for their first symptom: N = 10.</td>
</tr>
<tr>
<td>Patients excluded due to incomplete dates for their first symptom: N = 10.</td>
<td>Sex (of final sample): 2930 males, 1882 females.</td>
</tr>
<tr>
<td>Dysphagia: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years.</td>
<td>Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females.</td>
</tr>
<tr>
<td>Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample):</td>
<td>Rectal bleeding: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years.</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females.</td>
</tr>
<tr>
<td>All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.</td>
<td>Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.</td>
</tr>
<tr>
<td>Clinical setting: Primary care</td>
<td></td>
</tr>
</tbody>
</table>

#### Are there concerns that the included patients and setting do not match the review question? | Low concern |

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability
<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
</table>
| Reference standard(s) | Cancer code in the UK’s General Practice Research Database:  
Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs.  
Haemoptysis: Respiratory tract neoplasms.  
Dysphagia: Oesophageal neoplasms.  
Rectal bleeding: Colorectal neoplasms. |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear (but all patients had a positive index test) |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for in the results</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

- Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates.
- Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:  
  - Haematuria: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.  
  - Dysphagia: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men.  
  - Estimates based on the pre-specified cancers may be thus conservative for these symptoms.  
  - Haemoptysis: Extension of the diagnostic criteria yielded 6 additional cancers.  
  - Rectal bleeding: Extension of the diagnostic criteria yielded 2 additional
Muris (1995)

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 80/460 general practitioners in Limburg (The Netherlands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 933; 335 males, 598 females; age range = 18-75, aged &gt; 30 years: N = 712, aged &gt; 40 years: N = 517, aged &gt; 60 years: N = 171.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>GPs in The Netherlands</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? | High concern |

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>New abdominal complaints lasting ≥ 2 weeks. Not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | High concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up for ≥ 12 months (mean = 18 months).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING
### A. risk of bias

**Flow and timing**

All patients appear to be accounted for.

Was there an appropriate interval between index test and reference standard? **Unclear**

Did all patients receive the same reference standard? **Yes**

Were all patients included in the analysis? **Yes**

Could the patient flow have introduced bias? **Low risk**

### NOTES

Other cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), kidney (1/933), cervix (1/933), other cancer of the female genital system (2/933), and other and unspecified sites (2/933).

---

### Oudega (2006)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling

Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in The Netherlands.

Was a consecutive or random sample of patients enrolled? **Yes**

Was a case-control design avoided? **Yes**

Did the study avoid inappropriate exclusions? **Yes**

Could the selection of patients have introduced bias? **Low risk**

**B. Concerns regarding applicability**

Patient characteristics and setting

N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years.

Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis.

Exclusion criteria: Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis.

Clinical setting: Primary care, The Netherlands.

Are there concerns that the included patients and setting do not match the review question? **Unclear concern**

**INDEX TEST**

**A. Risk of bias**

Index test

Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis.

Were the index test results interpreted without knowledge of the results of the reference standard? **Yes**

Could the conduct or interpretation of the index test have introduced bias? **Low risk**

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Low concern**
**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
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<tbody>
<tr>
<td>Reference standard(s)</td>
<td>2 years follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
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<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
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<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
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**FLOW AND TIMING**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
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</tbody>
</table>

**NOTES**

In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

**References**

**Included studies**


Excluded studies (with excl reason)
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review

Not in PICO


Paper in Russian. Unclear whether relevant, but unlikely based on the short abstract there available in English.


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Duplicate


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO (referred patients)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Only published as abstract which doesn't allow the extraction of relevant data. Hopefully, the study will be published in full by the time the outdate search is done.

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Review identifying no papers in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Duplicate

Not in PICO

Not in PICO

Not in PICO

Not in PICO (outcome)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Guideline/not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Letter


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Systematic Review. The included studies are also included in our review.
Not in PICO
Not in PICO
Duplicate
Duplicate
Systematic review, included studies checked for relevance.
Not in PICO
Not in PICO
Sinnakirouchenan, R. & Ramalingam, V. (2012) All that wheezes is not asthma! Journal of Hospital Medicine, Conference: March.
Not in PICO
Journal of General Practice, 63: 47-54.
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO (for S&S or for tests)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Narrative review

Not in PICO

Not in PICO

Tanner, K., Roden, K., Hancock, J. & Morgan, A. (2014) Haemoptysis referrals with a normal CT scan can be seen safely in a monthly haemoptysis clinic results of a retrospective audit. Lung Cancer, 83: S33.
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO (for S7S and for tests)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO

**Review question:**

Which investigations of symptoms of suspected lung cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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Total References retrieved (after de-duplication): 487

**Update Search**

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No evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT, sputum cytology, or bronchoscopy in patients with suspected lung cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Paper in Russian. Unclear whether relevant based on the short abstract there available in English.


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO

Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO (secondary care)


Not in PICO


Narrative review


Not in PICO

Brady, M. J., Thomas, J., Wong, T. Z., Franklin, K. M., Ho, L. M. & Paulson, E. K. (2009) Adrenal nodules at FDG PET/CT in patients known to have or suspected of having lung cancer: a proposal...

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Duplicate


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


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Not in PICO


Not in PICO


Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review

Not in PICO

Not in PICO

Duplicate

Narrative review

Narrative review

Not in PICO

Ref Type: Generic
Ref ID: 548
Reprint: Not in File
Abstract: Presents the case of a 68-year-old man with lung cancer in remission, who was admitted to the oncology unit with increasing dyspnea. He reported symptoms that included shortness of breath, difficulty sleeping, and a lack of appetite. The patient's physician ordered supplemental oxygen and scheduled diagnostic imaging examinations, laboratory tests, and a possible bronchoscopy. The morning after admission, the patient experienced significantly increased dyspnea. The stress-management nurse realized that the sensation of breathlessness was creating panic, which increased anxiety and the need for oxygen, worsening the dyspnea. The stress-management nurse coached the patient in a structured relaxation technique as a tool to help him learn to control and regulate his breathing. Over time the response was positive, as reported by the patient and validated by the oncology nurse. Although dyspnea is a complex symptom that varies among patients, nonpharmacologic interventions to promote relaxation and provide instruction in breathing control may reduce stress and increase the ease and effectiveness of respiration and gas exchange. Nurses should be familiar with simple stress management approaches, such as relaxation breathing, to assist an anxious patient with ineffective breathing. (PsycINFO Database Record (c) 2012 APA, all rights reserved)
Notes: DB - PsycINFO
AN - Peer Reviewed Journal: 2008-04562-008
MA - Glennon, Cathy: cglennon@kumc.edu
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review
Narrative review

Not in PICO

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Narrative review

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Duplicate

Duplicate

Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


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Narrative review


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Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Protocol


Narrative review


Narrative review


Not in PICO


Already included


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Not in PICO


Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Duplicate


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Not in PICO (test positives only)


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review

In Japanese with no English abstract, but 7/15 references about screening, so probably not in PICO


Not in PICO


Not in PICO (screening)


Narrative review


Narrative review


Not in PICO


Not in PICO


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Not in PICO
Narrative review
Narrative review

Narrative review

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Narrative review

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Narrative review

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Very little patient information, but seems to be Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO (cancer casxes only)

Ongoing study

Not in PICO
Not in PICO
Narrative review
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO

Guideline/not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

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Narrative review

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Narrative review

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Narrative review

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Narrative review

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Narrative review

Narrative review

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Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Does not appear to be in PICO, but very little reporting on patients or methods.
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Not in PICO


Guideline


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not sure if narrative review as it is entirely in Japanese with no English abstract.


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO

neurological syndromes: Comparison of 18F-FDG PET/CT and contrast-enhanced CT. *European Journal of Nuclear Medicine and Molecular Imaging*, 40: 1014-1024.

Not in PICO


Systematic review, but any relevant individual studies will be included separately


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO

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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Narrative review
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Narrative review


Not in PICO


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Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review

Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Ref Type: Generic
Ref ID: 549
Reprint: Not in File

Abstract: Screening is not a test but a process. This distinction matters. Findings on radiographic screening lead to a diagnostic workup. Once a diagnosis is made, the process dictates the choice of treatment. Each of the steps in a screening algorithm is a medical decision in which the physician, acting as the patient's advocate, weighs benefits and risks. Physicians caring for people who are susceptible to lung cancer face four conflicting factors: the demand from the public to act, the need to consider cost-effectiveness and social responsibility, the need for scientific knowledge, and the lack of definitive evidence. One of the inherent weaknesses of any single radiographic or biomarker test for lung cancer is the inability to provide unequivocal information about the biology of a tumor - that is, its growth pattern and how it will respond to therapy. We are making solid progress in combining CT scanning with sputum analysis, fluorescence bronchoscopy, and analysis of pulmonary fluids, exhaled gases, and blood by genomic, proteomic, and immunologic methods. Routine clinical applications of these methods, however, are not available. These technological wonders require extensive validation and proof that markers alone or in combination are sufficiently specific for the detection and diagnosis of lung cancer. (PsycINFO Database Record (c) 2012 APA, all rights reserved)

Notes: DB - PsycINFO
AN - Peer Reviewed Journal: 2006-20691-005


Not in PICO (referred population)


Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

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Narrative review


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Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


In Chinese, with no English abstract.


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
MESOTHELIOMA

Review question:
What is the risk of mesothelioma in patients presenting in primary care with symptom(s)?

Results

Literature search

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Update Search

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Total References retrieved (after de-duplication): 5
Study results

No evidence was identified.

References

Included studies
None

Excluded studies (with excl reason)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Narrative review
Not in PICO
Narrative review
Not in PICO
Guideline
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review

Review question:
Which investigations of symptoms of suspected mesothelioma should be done with clinical responsibility retained by primary care?

Results

Literature search

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Study results

No evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT, abdominal x-ray, or ultrasound in patients with suspected mesothelioma where the clinical responsibility was retained by primary care.

References

Included studies
None
Excluded studies (with excl reason)
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Not in PICO
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO


Ferretti, G. (2011) [What are the tools for post-occupational follow-up, how should they be performed and what are their performance, limits and benefit/risk ratio? Chest X-Ray and CT scan]. [Review] [French]. *Revue des Maladies Respiratoires*, 28: 761-772.


1149.
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Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


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### UPPER GASTRO-INTESTINAL TRACT CANCERS

#### OESOPHAGEAL

**Review question:**
What is the risk of oesophageal cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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Total References retrieved (after de-duplication): 294

**Update Search**

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Total References retrieved (after de-duplication): 21
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in setting that may not directly translate to UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity. The evidence base is also limited by the fact that some of the positive predictive value estimates are based on low numbers of patients and a number of the studies do not provide different estimates for stomach and oesophageal cancer, but only provide one estimate for these cancers combined.
Study results

Table 1: Oesophageal cancer: Meta-analyses

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<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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<th>Patient group</th>
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<td>Tosetti (2010)</td>
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<td>Vakil (2009)</td>
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<tr>
<td>Study</td>
<td>Symptom(s)</td>
<td>Patient group</td>
<td>PPVs % (95% CI); prevalence</td>
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<td>Collins (2012)</td>
<td>Abdominal pain</td>
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<td>Collins (2012)</td>
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<td>All patients</td>
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<td>Droogendijk (2011)</td>
<td>Anaemia</td>
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<td>Brignoli (1997)</td>
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<td>Duggan (2008)</td>
<td>Dyspepsia</td>
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<td>Thomson (2003)</td>
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<tr>
<td>Vakil (2009)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td></td>
</tr>
</tbody>
</table>

Please note that the data from Stapley (2013) are not included in these meta-analyses due to the case-control design of the study, and the data from Mahadeva (1998) is not included due to the limited and different age range of the population. These data are instead reported in the table below entitled “Additional results reported by the individual papers: Single symptoms”. When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead.
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
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Table 3: Oesophageal cancer: Additional results reported by the individual papers: Single symptoms
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<td>Stapley (2013)</td>
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<td>Stapley (2013)</td>
<td>Epigastric pain</td>
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<td>Vakil (2009)</td>
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<td>Hippisley-Cox (2011)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>1.2</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Weight loss</td>
<td>Patients ≥ 55 years</td>
<td>0.9</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Haematemesis</td>
<td>All patients</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Table 4: Oesophageal cancer: Additional results reported by the individual papers: Symptom combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Haematemesis</td>
<td>All patients</td>
<td>2.3 (1.9-2.7) 101/4477</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation</td>
<td>Patients ≥ 55 years</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.6-0.7)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Nausea and/or vomiting ≥ 2 weeks</td>
<td>All patients</td>
<td>0 (0-12.3)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting reported ≥ twice</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.5 (0.4-0.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>5.8 (3.5-10.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>9.2 (4.4-22.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>6.5 (3.5-13.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>9.3 (NR)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and reflux</td>
<td>Patients ≥ 55 years</td>
<td>5 (3.3-8.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>4.6 (3.4-6.6)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>7.3 (4.4-13.9)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and jaundice</td>
<td>All patients</td>
<td>0 (0-48.32) 0/6</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and black stools</td>
<td>All patients</td>
<td>0.91 (0.05-5.69) 1/110</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and bloody stools</td>
<td>All patients</td>
<td>0.76 (0.04-4.81) 1/131</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>5.8 (3.5-10.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>9.2 (4.4-22.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>6.5 (3.5-13.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>9.3 (NR)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and reflux</td>
<td>Patients ≥ 55 years</td>
<td>5 (3.3-8.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>4.6 (3.4-6.6)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>7.3 (4.4-13.9)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and dysphagia</td>
<td>All patients</td>
<td>1.4 (0.04-4.36) 3/215</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and dyspepsia</td>
<td>Patients ≥ 55 years</td>
<td>9.8 (5.7-20.2)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptom Combination</td>
<td>Age Group</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------</td>
<td>------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>6.1 (3.2-13.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.7-1.3)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (1-2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and weight loss</td>
<td>All patients</td>
<td>1.37 (0.35-4.28)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>2.1 (1.3-3.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and anaemia</td>
<td>All patients</td>
<td>0 (0-11.71)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.3)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>1.1 (0.8-1.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>0.4 (0.3-0.5)</td>
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<td>Stapley (2013)</td>
<td>Constipation and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (0.8-2.3)</td>
</tr>
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<td>Stapley (2013)</td>
<td>Constipation and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.5-1.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.4 (0.4-0.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.4-0.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and dyspepsia</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and dysphagia</td>
<td>Patients ≥ 55 years</td>
<td>4.2 (2.7-7.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea</td>
<td>All patients</td>
<td>0 (0-1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/293</td>
</tr>
<tr>
<td>Study and Year</td>
<td>Symptoms and Signs</td>
<td>Age Group</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.5 (0.4-0.6)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-21)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea/vomiting &gt; 2 weeks and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-44)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea/vomiting &gt; 2 weeks and weight loss/anorexia</td>
<td>All patients</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and weight loss/anorexia and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-20)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and reflux</td>
<td>Patients ≥ 55 years</td>
<td>1.5 (1-2.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>4.2 (1.8-11)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1.6 (1.1-2.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>3.1 (1.5-6.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Weight loss and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.3)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia</td>
<td>All patients</td>
<td>0 (0-80)</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Symptom(s)</td>
<td>Patient Group</td>
<td>Proportion</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia and gastrointestinal bleeding and nausea/vomiting &gt; 2 week</td>
<td>All patients</td>
<td>0 (0-16.6) / 0/25</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia and nausea/vomiting &gt; 2 week</td>
<td>All patients</td>
<td>0 (0-80) / 0/2</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>2.8 (1.7-4.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>1.3 (0.9-2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and reflux</td>
<td>Patients ≥ 55 years</td>
<td>2.3 (1.5-3.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.6 (0.9-2.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Weight loss and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.8 (1.1-3)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (1-2.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.9 (1-3.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Low haemoglobin and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.6-0.7)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + previous dyspepsia</td>
<td>All patients</td>
<td>0 (0-0.62) / 0/773</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + no previous dyspepsia</td>
<td>All patients</td>
<td>0 (0-0.91) / 0/524</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + unchanged previous dyspepsia</td>
<td>All patients</td>
<td>0 (0-1.2) / 0/407</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + no previous or changed dyspepsia</td>
<td>All patients</td>
<td>0 (0-0.54) / 0/890</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + pain provoked by meals</td>
<td>All patients</td>
<td>0 (0-1.8) / 0/257</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + no pain provoked by meals</td>
<td>All patients</td>
<td>0 (0-0.52) / 0/924</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + relief of pain by meals</td>
<td>All patients</td>
<td>0 (0-0.7) / 0/488</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + no pain</td>
<td>All patients</td>
<td>0 (0-2.8) / 0/687</td>
</tr>
</tbody>
</table>
relief by meals

<table>
<thead>
<tr>
<th>Møllmann (1981)</th>
<th>Any of the inclusion symptoms + irritable bowel syndrome</th>
<th>All patients</th>
<th>0 (0-2.8)</th>
<th>0/167</th>
</tr>
</thead>
<tbody>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + no irritable bowel syndrome</td>
<td>All patients</td>
<td>0 (0-0.42)</td>
<td>0/1129</td>
</tr>
</tbody>
</table>

Please note:
- The calculations of the positive predictive values differ between the all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = not reported.

Evidence statement(s):

Abdominal pain (4 studies, N = 3416339) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.3% for oesophageal cancer. The studies were associated with 0-3 bias or applicability concerns (see also Tables 1-3).

Anaemia (8 studies, N = 3417170) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.94% for oesophageal cancer. The studies were associated with 0-4 bias or applicability concern (see also Tables 1-3).

Dyspepsia (13 studies, N = 52183) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.2% for oesophageal cancer. The studies were associated with 1-3 bias or applicability concerns (see also Tables 1-3).

Dysphagia (5 studies, N = 4177284) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.5% for oesophageal cancer. All the studies were associated with 0-1 bias or applicability concerns (see also Tables 1-3).

Other single symptoms (6 studies, N = 3417192) presenting in a primary care setting are associated with an overall positive predictive values for oesophageal cancer up to 2.3% (for haematemesis). The studies were associated with 0-4 bias or applicability concerns (see also Table 3).

Two or more symptom presenting in combination (3 studies, N = 43319) in a primary care setting are associated with overall positive predictive values for oesophageal cancer up to to 9.8% (for dysphagia and dyspepsia). The studies were associated with 1-3 bias or applicability concerns (see also Table 4).

Evidence tables

Brignoli (1997)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

| **B. Concerns regarding applicability** |
### Patient characteristics and setting

N = 828; 329 men, 499 women; mean (SD) age = 41-42 (15-16) years.

**Inclusion criteria**: “Adult patients with epigastric complaints were admitted to the multicentre [omega]-project if their symptoms persisted for over 1 month and their clinical history and appearance did not suggest an organic disorder (i.e. absence of alarm features, such as gastrointestinal blood loss, palpable tumour mass, massive weight loss, etc.). The studies were conducted by general practitioners acting as primary care physicians.”

**Exclusion criteria**: None listed

**Clinical setting**: Primary care, Switzerland

---

### Are there concerns that the included patients and setting do not match the review question?

| Unclear concern |

### INDEX TEST

#### A. Risk of bias

**Index test**

Epigastric complaints (dyspepsia)

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**

Endoscopy and 84-day follow up.

**Is the reference standard likely to correctly classify the target condition?**

No

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

No

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

High risk

### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

Low concern

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**

All patients are accounted for

**Was there an appropriate interval between index test and reference standard?**

Yes

**Did all patients receive the same reference standard?**

Yes

**Were all patients included in the analysis?**

Yes

**Could the patient flow have introduced bias?**

Low risk

### NOTES

3 patients had gastric cancer, 0 patients had oesophageal cancer, and 2 patients had cancer outside the digestive tract.
## PATIENT SELECTION

### A. risk of bias

**Patient sampling**
- Retrospective patient series using the THIN database.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>A total of 2135540 patients were identified from 364 practices.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms:</strong></td>
<td>Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women).</td>
</tr>
<tr>
<td>Incident cases of gastro-oesophageal cancer during the 2-year follow up period:</td>
<td>N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer).</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

**Exclusion criteria:**
- Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates.

| Clinical setting | Primary care, UK |

**Are there concerns that the included patients and setting do not match the review question?**
- Low concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th><strong>Index test</strong></th>
<th>‘Red-flag’ symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th><strong>Reference standard(s)</strong></th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear
---|---
Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern

**FLOW AND TIMING**

**A. risk of bias**

Flow and timing | All patients seem to be accounted for
Was there an appropriate interval between index test and reference standard? | Yes
Did all patients receive the same reference standard? | Yes
Were all patients included in the analysis? | Yes
Could the patient flow have introduced bias? | Low risk

**NOTES**

The study did not distinguish between gastric and oesophageal cancer

---

**Droogendijk (2011)**

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling | Retrospective peripheral hospital laboratory database study serving 265 GPs in Dordrecht (Holland).
Was a consecutive or random sample of patients enrolled? | Yes
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting | N = 287; 129 men, 158 women; median (range) age = 70 (19-87) years.
Inclusion criteria: All women aged > 50 years and all men aged ≥ 18 years who between January 2004 and December 2005 were diagnosed with iron-deficiency anaemia (haemoglobin < 13.7 g/dl in men and < 12.1 g/dl in women, and a serum ferritin level < 25 µg/l for men and < 20 µg/l for women).
Exclusion criteria: Patients with a known history of iron-deficiency anaemia in the previous 2 years, a history of gastrointestinal malignancy or congenital haemoglobinopathy.
Clinical setting: GPs in Holland
Are there concerns that the included patients and setting do not match the review question? | Unclear concern

**INDEX TEST**

**A. Risk of bias**

Index test | New onset iron-deficiency anaemia (haemoglobin < 13.7 g/dl in men and < 12.1 g/dl in women, and a serum ferritin level < 25 µg/l for men and < 20 µg/l for women).
 Were the index test results interpreted without knowledge | Yes
<table>
<thead>
<tr>
<th>Reference(s) standard(s)</th>
<th>Endoscopy and 12-month follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>It is unclear if all patients are accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>Yes</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

In addition to the 24 patients with colorectal cancer, 3 patients had gastric cancer, 1 patient had oesophageal cancer and 1 patient had locally invasive endometrial cancer.

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Prospective patient series from 43 GP practices in the UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 762; 411 men, 351 women; mean (range) age = 42 (18-73) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients aged 18-70 with dyspepsia thought by the GP to arise from the upper GI tract and of sufficient severity to justify empirical treatment with an H₂ antagonist or PPI.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Patients thought to be unfit for investigation, with alarm...</td>
</tr>
</tbody>
</table>
Symptoms suggestive of malignancy (dysphagia, weight loss > 5 g, anaemia, haematemesis, melena or jaundice), previous radiological or endoscopic diagnosis of peptic ulcer disease or reflux oesophagitis, investigation for dyspepsia in the previous 5 years with either procedure or symptom onset within 6 months of commencement of NSAID therapy, previous H. pylori eradication therapy or more than 3 prescriptions for acid suppression therapy in the previous 6 months.

Clinical setting: Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

Dyspepsia

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

**REFERENCE STANDARD**

A. Risk of bias

Reference standard(s)

Endoscopy and 1-2-year follow up.

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? No

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

**FLOW AND TIMING**

A. Risk of bias

Flow and timing

At 12-month follow up GP data were available for 753/762.

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Low risk

**NOTES**

2 patients had gastric cancer, 2 patients had oesophageal cancer (the authors report that these patients should not have been included as they had a history of dysphagia).

Edenholm (1985)

**PATIENT SELECTION**
### A. Risk of bias

**Patient sampling**
Prospective patient series from the District General Clinic in Huskvarna, Sweden.

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

**Patient characteristics and setting**
N = 187; 96 men, 91 women; mean/median (range) age = 44 (17-80) years.

- **Inclusion criteria**: Patients who between November 1982 and June 1984 called on the clinic because of abdominal pain and who were diagnosed by the general practitioner as having ulcer-like dyspepsia. The criterion used was persistent epigastric pain. Most patients also had additional symptoms such as acid regurgitation, nausea, belching or vomiting.
- **Exclusion criteria**: None listed
- **Clinical setting**: GPs in Sweden

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

**Index test**
Ulcer-like dyspepsia. The criterion used was persistent epigastric pain.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**
UGI endoscopy

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**
20/187 patients declined endoscopy and it was unsuccessful in a further 2 patients. Thus the PPV is likely to be an over-estimate, calculated as 2/165.

| Was there an appropriate interval between index test and reference standard? | Yes probably |
| reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | No |
| Could the patient flow have introduced bias? | High risk |
| NOTES | There were a total of 3 cancers confirmed in the 165 patients who received UGI endoscopy: 1 oesophageal cancer, 1 stomach cancer, and 1 cancer of the duodenum, the latter of which was included with the stomach cancer |

**PATIENT SELECTION**

### A. risk of bias

- **Patient sampling**
  - Prospective/retrospective? patient series from USA
- **Was a consecutive or random sample of patients enrolled?** Yes
- **Was a case-control design avoided?** Yes
- **Did the study avoid inappropriate exclusions?** Yes
- **Could the selection of patients have introduced bias?** Low risk

### B. Concerns regarding applicability

- **Patient characteristics and setting**
  - N = 100; 49 men, 51 women; mean (SE) age = 64 (2) years.
  - **Inclusion criteria**: Patients with new onset dysphagia without a prior work up who were evaluated at the Cleveland Clinic Foundation outpatient clinic by their primary care physician.
  - **Exclusion criteria**: Neurological disease, oropharyngeal dysphagia or previous gastric or oesophageal surgery, and patients without a final diagnosis explaining their dysphagia.
  - **Clinical setting**: Primary care outpatient clinic, USA.

**INDEX TEST**

### A. Risk of bias

- **Index test**
  - New onset dysphagia
- **Were the index test results interpreted without knowledge of the results of the reference standard?** Yes
- **Could the conduct or interpretation of the index test have introduced bias?** Low risk

### B. Concerns regarding applicability

- **Are there concerns that the index test, its conduct, or its interpretation differ from the review question?** Low concern

**REFERENCE STANDARD**

### A. risk of bias

- **Reference standard(s)**
  - Completed clinical and diagnostic testing after an initial barium swallow/upper GI endoscopy.
- **Is the reference standard likely to correctly classify the target condition?** Yes
- **Were the reference standard results interpreted without knowledge of the results of the index tests?** No
- **Could the reference standard, its conduct, or its interpretation have introduced bias?** Low risk
Suspected Cancer: Appendix F (June 2015)

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

6 patients had malignancy, but the type of malignancy was not further specified.

Farrus Palou (2000)

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Retrospective consecutive patient series from urban general practice covering a population of 24000.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 87 of whom the data from 29 were unavailable as no etiological diagnosis was found (due to patient refusal of further investigation [?; 8], lost to follow up [7], patient deterioration rendering them unsuitable for further investigation [14]); of the remaining 58 patients there were 14 males, 44 females; mean? (SD?) age = 54.26 (19.95) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients aged &gt; 14 years who attended the health centre between 1 October 1995 and 31 September 1996 who were found to have new onset (previously unknown) anaemia (haemoglobin &lt; 13 g/dl for men and 12 g/dl for women).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Pregnant women.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Spanish GP</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Anaemia (haemoglobin &lt; 13 g/dl for men and 12 g/dl for women)</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

#### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
</tbody>
</table>

#### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

**NOTES**

This paper is published in Spanish. One patient had gastric cancer, 2 patients had colon cancer.

### Hallissey (1990)

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2585 aged &gt; 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.</td>
</tr>
</tbody>
</table>

**Inclusion criteria:** All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia

**Exclusion criteria:** None listed.

**Clinical setting:** Primary care, England.

<p>| Are there concerns that the included patients and setting | Unclear concern |</p>
<table>
<thead>
<tr>
<th><strong>do not match the review question?</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>Dyspepsia of any degree</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Upper gastrointestinal endoscopy within 4 weeks and follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>2659 patients were seen and 2585 attended for investigation</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).</td>
</tr>
<tr>
<td>Hansen (1998)</td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series from general an open-access endoscopy clinic in Denmark.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Did the study avoid inappropriate exclusions? Yes

Could the selection of patients have introduced bias? Low risk

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 612 from 66 GPs; 288 males / 324 females; mean age (SD) = 47 (16.8) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>“All general practitioners (n = 108) in the city of Odense (population, 170,000) were invited to participate in the study. GPs were asked to refer all patients who consulted them with dyspepsia, regardless of the severity of the symptoms. To obtain compliance with this request the participating GPs were sent numerous reminders. Because of a limited endoscopy capacity not all GPs took part in the study at the same time.” Study period was 11 March 1991-27 March 1992.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Aged &lt; 18 years, signs of UGI bleeding, abdominal emergency, jaundice, previous surgery in the UGI tract except for closure of an ulcer, supposed acute bacterial or viral infection, pregnancy, or endoscopy contraindicated.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>GPs in Denmark</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? Unclear concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Epigastric or retrosternal pain or discomfort, with or without heartburn, nausea, vomiting, and any other symptom considered to be referable to the proximal alimentary tract.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Could the conduct or interpretation of the index test have introduced bias? Low risk

#### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Endoscopy within 1 week of referral and follow up</th>
</tr>
</thead>
</table>

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? No

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

#### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

### FLOW AND TIMING

#### A. Risk of bias

| Flow and timing | 56 eligible patients declined participation. These patients were older than |
the study group (mean age = 52 years versus 47 years) and they were characterised by a shorter dyspepsia history (median duration = 1 month, range = 4 days to 35 years versus 2 months, range = 4 days to 14 years). Fewer of the non-participating patients had had a previous endoscopy or UGI radiography (22% versus 43%, but identical proportions of the patients had an ulcer history (11% versus 14%).

Was there an appropriate interval between index test and reference standard? Yes
Did all patients receive the same reference standard? Yes
Were all patients included in the analysis? No
Could the patient flow have introduced bias? Unclear risk

NOTES
There were a total of 4 cancers histologically confirmed in the study. No subclassification of the cancers reported. Follow up of the 364 patients with normal endoscopy revealed missing date in 5% of the cases and 1 lymphoma and 1 rectal carcinoma. These 6 cancers (NOS) are included in the overall PPV for dyspepsia.

Heikkinen (1995)

PATIENT SELECTION

A. risk of bias

Patient sampling
Consecutive patient series from 11 GPs (from 3 rural health centres) and from the catchment area of 6 physicians in the health centre of an urban area (population [individuals > 14 years old] of study area = 24600) in Finland.

Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk

B. Concerns regarding applicability

Patient characteristics and setting
N = 400; 152 males, 248 females; 77% were > 44 years.

Inclusion criteria: Consecutive patients who consulted their GP from January 11th 1993 to January 12th 1994 for dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

Exclusion criteria: Patients with symptoms of an acute condition within the abdomen or who had had an upper intestinal endoscopy performed within the last 3 months or aged < 15 years

Clinical setting: Primary care, Finland.

Are there concerns that the included patients and setting do not match the review question? Unclear concern

INDEX TEST

A. Risk of bias

Index test
Dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

Were the index test results interpreted without knowledge of the results of the reference standard? Yes
### Could the conduct or interpretation of the index test have introduced bias?

**Low risk**

### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

**Low concern**

### REFERENCE STANDARD

**A. risk of bias**

**Reference standard(s)**

Upper gastrointestinal endoscopy, upper abdominal ultrasound, more detailed interview, blood count, serum screening (creatinine, alkaline phosphatise, alanine aminotransferase, amylase, and C-reactive protein), lactose intolerance test, and follow up of ≥ 1 month.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?

**Low concern**

### FLOW AND TIMING

**A. risk of bias**

Flow and timing

All patients appear to be accounted for.

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### NOTES

In total N = 9 had cancer: 0 colorectal, 2 oesophageal and 7 stomach (of which 3 were lymphomas of the MALT type (Mucosa-associated lymphoid tissue).  

Hippisley-Cox (2011)

### PATIENT SELECTION

**A. risk of bias**

Patient sampling

Prospective patient series using patients in the QResearch database (version 30).

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Patient characteristics and setting

A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6).  
Symptoms:  
Current dysphagia (N = 8165), current haematemesis (N = 7119), current
abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the last year (N = 218862.

Incident cases of gastro-oesophageal cancer during the 2-year follow up period:
N = 1343 (776 oesophageal and 567 gastric).

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care, UK

| Are there concerns that the included patients and setting do not match the review question? | Low concern |
| INDEX TEST |  |
| A. Risk of bias |  |
| Index test | ‘Red-flag’ symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |
| B. Concerns regarding applicability |  |
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

| REFERENCE STANDARD |  |
| A. risk of bias |  |
| Reference standard(s) | 2-year follow up |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |
| B. Concerns regarding applicability |  |
Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern

FLOW AND TIMING
A. risk of bias

| Flow and timing | A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives. |

| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | No |
| Could the patient flow have introduced bias? | Unclear risk |

NOTES
Results not presented separately for gastric and oesophageal cancer

Jaskiewicz (1991)

PATIENT SELECTION
A. risk of bias

| Patient sampling | Patient series from a program aimed at screening patients with chronic gastric complaints for gastric carcinoma in the South and North-Western Cape Province of South Africa. |

| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Unclear |
| Could the selection of patients have introduced bias? | Unclear risk |

B. Concerns regarding applicability

| Patient characteristics and setting | N = 585, 355 males, 230 females; mean (range) age males = 45.1 (19-87) years, mean (range) age females = 47.2 (19-87) years. |

Inclusion criteria: “participants who were treated for dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months. Patients represented various areas in the south and north-western Cape province including Namaqualand, and formed part of a programme aimed at screening patients with chronic gastric complaints for gastric carcinoma.”

Exclusion criteria: None listed

Clinical setting: Unclear, South Africa.

Are there concerns that the included patients and setting do not match the review question? | Unclear concern

INDEX TEST
A. Risk of bias

<p>| Index test | Unspecified dyspepsia (dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months). |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>NOTES</td>
<td>In total N = 16 had gastric cancer. No oesophageal cancers reported</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td></td>
</tr>
<tr>
<td>PATIENT SELECTION</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years. Number of first occurrences in patients with no previous diagnosis of cancer: Haematuria: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females.</td>
</tr>
</tbody>
</table>
**Haemoptysis**: \( N = 4822 \), mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: \( N = 10 \). Sex (of final sample): 2930 males, 1882 females.

**Dysphagia**: \( N = 6003 \), mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: \( N = 4 \). Sex (of final sample): 2628 males, 3371 females.

**Rectal bleeding**: \( N = 15314 \), mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: \( N = 25 \). Sex (of final sample): 7523 males, 7766 females.

**Inclusion criteria**: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.

**Exclusion criteria**: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.

**Clinical setting**: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear (but all patients had a positive index test)</td>
</tr>
</tbody>
</table>
Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk
---|---

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern
---|---

FLOW AND TIMING

A. Risk of bias

Flow and timing: All patients are accounted for in the results.

Was there an appropriate interval between index test and reference standard? | Unclear
---|---

Did all patients receive the same reference standard? | Yes
---|---

Were all patients included in the analysis? | Yes
---|---

Could the patient flow have introduced bias? | Low risk
---|---

NOTES

Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates.

Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:

- **Haematuria**: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.

- **Dysphagia**: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women [reported in the paper, however, the numbers reported do not match up and I think the PPV is instead 2.91%; 98/3371] and 6.9% in men.

- **Estimates based on the pre-specified cancers may be thus conservative for these symptoms.**

- **Haemoptysis**: Extension of the diagnostic criteria yielded 6 additional cancers.

- **Rectal bleeding**: Extension of the diagnostic criteria yielded 2 additional cancers.

Kagevi (1989)

PATIENT SELECTION

A. Risk of bias

Patient sampling: Prospective consecutive patient series from a primary care centre in Sweden.

Was a consecutive or random sample of patients enrolled? | Yes
---|---

Was a case-control design avoided? | Yes
---|---

Did the study avoid inappropriate exclusions? | Yes
---|---

Could the selection of patients have introduced bias? | Low risk
---|---

B. Concerns regarding applicability
**Patient characteristics and setting**  
N = 172; 88 men, 84 women; mean (SD) age = 43 (16) years.

**Inclusion criteria:** “All patients visiting the medical center with complaints referable to the digestive tract were considered for inclusion. Even when the patient consulted the primary care center because of another complaint and coincidentally mentioned gastrointestinal problem, the patient was considered for inclusion. The patient’s gastrointestinal problem could have been reported in connection with an earlier visit at the primary care center.”

**Exclusion criteria:** Patients with jaundice, gastrointestinal bleeding or acute abdominal pain were excluded and so were patients judged to have a non-gastro-enterologic cause of their symptoms (gynaecologic problems, spondylosis deformans, etc), patients aged < 16 years and patients unwilling to participate.

**Clinical setting:** Primary care Center, Sweden.

---

**Are there concerns that the included patients and setting do not match the review question?**  
Unclear concern

---

### INDEX TEST

#### **A. Risk of bias**

**Index test**  
Dyspepsia defined as any pain, discomfort, or other symptoms referable to the digestive tract ≥ 2 weeks. Symptoms could be intermittent or continuous.

**Were the index test results interpreted without knowledge of the results of the reference standard?**  
Yes

**Could the conduct or interpretation of the index test have introduced bias?**  
Low risk

#### **B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**  
Low concern

---

### REFERENCE STANDARD

#### **A. Risk of bias**

**Reference standard(s)**  
Esophagastroduodenoscopy within 1 week and 6 month follow up.

**Is the reference standard likely to correctly classify the target condition?**  
Yes

**Were the reference standard results interpreted without knowledge of the results of the index tests?**  
No

**Could the reference standard, its conduct, or its interpretation have introduced bias?**  
Low risk

#### **B. Concerns regarding applicability**

**Are there concerns that the target condition as defined by the reference standard does not match the question?**  
Low concern

---

### FLOW AND TIMING

#### **A. Risk of bias**

**Flow and timing**  
13/185 patients were excluded as they did not want to have an endoscopy

**Was there an appropriate interval between index test and reference standard?**  
Yes

**Did all patients receive the same reference standard?**  
Yes

**Were all patients included in the analysis?**  
Yes

**Could the patient flow have introduced bias?**  
Low risk
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from the Primary Care Clinics of the University of Malaya in Malaysia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 432; 198 males/234 females; mean ages (SDs) = 30-31 (8) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: “All patients were recruited from the Primary Care Clinics of the University of Malaya, which provide a regular service to the local community. Patients aged ≤ 45 years presenting with uninvestigated dyspepsia were invited to participate in the study”, which ran from January 2004 until October 2005.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Age &gt; 45 or &lt; 18 years; symptoms of weight loss, progressive dysphagia or those suggestive of anaemia; pregnancy; previous H pylori testing; any contra-indication to to endoscopy or sedation; failure to turn up for initial test ; and on regular doses of non-steroidal anti-inflammatory drugs.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care clinic, Malaysia</td>
<td></td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question?  
High concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Uninvestigated dyspepsia. Dyspepsia defined as predominant upper abdominal discomfort for &gt; 4 weeks, with any associated symptoms, including heart burn and regurgitation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up ± upper endoscopy (oesophagogastrroduodenoscopy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
</tbody>
</table>

#### Could the reference standard, its conduct, or its

| Low risk |
| **B. Concerns regarding applicability** |  |
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

**FLOW AND TIMING**

| **A. risk of bias** |  |
| Flow and timing | 39/471 eligible patients were excluded from the study for the following reasons: 34/39 patients declined to participate, 3/39 became pregnant before the test, 1/39 emigrated from the country and 1/39 had missing data. |
| **Was there an appropriate interval between index test and reference standard?** | Yes |
| **Did all patients receive the same reference standard?** | Yes |
| **Were all patients included in the analysis?** | Yes |
| **Could the patient flow have introduced bias?** | Low risk |

**NOTES**

One patient was found to have cancer, which was metastatic pancreatic cancer. No oesophageal or gastric cancers were reported.

Meineche-Schmidt (2002)

**PATIENT SELECTION**

| **A. risk of bias** |  |
| Patient sampling | Consecutive patient series from 82 GPs in Denmark. |
| **Was a consecutive or random sample of patients enrolled?** | Yes |
| **Was a case-control design avoided?** | Yes |
| **Did the study avoid inappropriate exclusions?** | Yes |
| **Could the selection of patients have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 1491; 688 males, 803 females; age groups: 18-37 years: N = 377; 38-50 years: N = 369; 51-64 years: N = 338; 65+ years: N = 402. |
| **Inclusion criteria:** | Consecutive patients who consulted their GP between June 1991 and May 1993 for dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract). |
| **Exclusion criteria:** | None listed. |
| **Clinical setting:** | Primary care, Denmark. |

**Are there concerns that the included patients and setting do not match the review question?**

**UNCLEAR CONCERN**

**INDEX TEST**

| **A. Risk of bias** |  |
| **Index test** | Dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract). |
| **Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

<p>| <strong>Are there concerns that the index test, its conduct, or its interpretation have introduced bias?</strong> | Low concern |</p>
<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>18 months-3 years and 10 months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

**FLOW AND TIMING**

**A. risk of bias**

Flow and timing All patients appear to be accounted for

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Low risk

**NOTES**

In total N = 31 had cancer: 17 colorectal, 8 gastro-oesophageal (no subgroup analyses presented for these patients) and 6 other.

---

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling Prospective consecutive patient series from 11 general practitioners in Maastricht (Holland)

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

Could the selection of patients have introduced bias? Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting N = 578; 212 males, 342 females; age groups: 18-39 years: N = 295; 40-49 years: N = 80; 50-59 years: N = 91; 60-75 years: N = 88.

Inclusion criteria: Patients who during a 3-month period consulted one of the participating GPs for abdominal complaints.

Exclusion criteria: Patients aged < 18 years and patients with a condition necessitating immediate referral or admission to hospital.

Clinical setting: GPs in Holland

Are there concerns that the included patients and setting do not match the review question? Unclear concern
### A. Risk of bias

#### Index test
- Abdominal complaints. Not further specified, but the authors do report that the duration of pain before the patient presented for the first time for the evaluation of abdominal pain varied from some days to more than 1 year.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability
- Unclear concern

### REFERENCE STANDARD

#### A. Risk of bias
- Follow up for 15 months.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability
- Low concern

### FLOW AND TIMING

#### A. Risk of bias
- All patients appear to be accounted for.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES
- Although not explicitly stated by the authors it is implied that the patients included were those presenting with the abdominal complaint for the first time.

### Møllmann (1981)

### PATIENT SELECTION

#### A. Risk of bias
- Prospective patient series from an open-access gastroscopy clinic in Denmark.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

### Patient characteristics and setting

N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years N = 47; 90-99 years: N = 8.

Inclusion criteria: All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).

Exclusion criteria: Patients who had been examined for any of the above symptoms within the last 6 months.

**Clinical setting:** GPs in Denmark

### Are there concerns that the included patients and setting do not match the review question?

**Unclear concern**

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Upper abdominal pain &gt; 2 weeks, nausea and/or vomiting &gt; 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb &lt; 80%).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong> Yes <strong>Could the conduct or interpretation of the index test have introduced bias?</strong> Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-stage process: Gastroscopy with photography, using a gastroscope, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Is the reference standard likely to correctly classify the target condition?</strong> Unclear <strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong> No <strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong> Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong> Yes probably</td>
</tr>
</tbody>
</table>

Suspected Cancer: Appendix F (June 2015)  Page 170 of 1735
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**NOTES**
There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported.
This research was published in 2 papers.

**Stapley (2013)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong> Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong> The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | **Cases:** Oesophageal cancer cases: N = 4854, 3174 males / 1680 females; aged 40-54 years: N = 387; 55-69 years: N = 1712; 70-84 years: N = 2230; ≥ 85 years: N = 532. Gastric cancer cases: N = 2617, 1625 males / 992 females; aged 40-54 years: N = 130; 55-69 years: N = 671; 70-84 years: N = 1437; ≥ 85 years: N = 382. Median number of consultations (all cases) = 26 (IQR = 15-42) Controls: Oesophageal cancer controls: N = 21506, gender not reported; aged 40-54 years: N = 1539; 55-69 years: N = 7473; 70-84 years: N = 10296; ≥ 85 years: N = 2198. Gastric cancer controls: N = 11371, gender not reported; aged 40-54 years: N = 497; 55-69 years: N = 2887; 70-84 years: N = 6431; ≥ 85 years: N = 1556. Median number of consultations (all controls) = 15 (IQR = 7-28) Inclusion criteria: Cases: Patients with a record of one of 42 (18 oesophageal, 24 gastric) GPRD tumour diagnostic codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a oesophago-gastric cancer code was assigned the data of diagnosis/index date. Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. |

Suspected Cancer: Appendix F (June 2015)
**Exclusion criteria:** Oesophago-gastric cancer (controls), no consultations in the year before diagnosis. Clinical setting: Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?**

| | Low concern |

**INDEX TEST**

**A. Risk of bias**

**Index test**

All symptoms, physical signs or abnormal investigations compiled from the oesophago-gastric cancer literature were studied, and supplemented by literature from relevant cancer websites. The GPRD’s code list has many synonyms for similar symptoms, often including additional description such as severity or duration. These synonyms were identified and merged. The dyspepsia variable merged codes with either the word ‘dyspepsia’ or ‘indigestion’; the reflux variable included ‘regurgitation’ as well as ‘reflux’; the variable ‘epigastric pain’ required a precise anatomical description, whereas the variable ‘abdominal pain’ incorporated all other abdominal pain variables without a precise anatomical description. Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. For laboratory tests, the local laboratory range was used to identify abnormal results. Patients without a test were considered to be the same status as those with a normal result. All hepatic enzyme results were merged into a composite variable, deemed abnormal if any enzyme was raised; similarly, abnormal erythrocyte sedimentation rate, plasma viscosity and C-reactive protein were collated into a single variable called raised inflammatory markers. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal).

Were the index test results interpreted without knowledge of the results of the reference standard? **Yes**

*For diagnostic case-control studies:* Investigators were kept 'blind' to other important confounding and prognostic factors? **Yes**

Could the conduct or interpretation of the index test have introduced bias? **Low risk**

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? **Low concern**

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**

Oesophago-gastric cancer code in the UK’s General Practice Research Database.

Is the reference standard likely to correctly classify the target condition? **Yes**

Were the reference standard results interpreted without knowledge of the results of the index tests? **Unclear**

Could the reference standard, its conduct, or its interpretation have introduced bias? **Low risk**

**B. Concerns regarding applicability**
**Are there concerns that the target condition as defined by the reference standard does not match the question?**

Low concern

### FLOW AND TIMING

**A. risk of bias**

**Flow and timing**

A total of 45356 patients were identified, 37699 controls and 7657 cases. Of the controls the following exclusions were applied: Already used as a case (N = 252), case excluded (N = 808), duplicate control (N = 427) and no data in year pre-index date (N = 3335). Of the cases the following exclusions were applied: No controls (N = 17), OG cancer diagnosis before 2000 (N = 28), case already used as case (for other O/G cancer: N = 131) and case with metastatic cancer (N = 10).

**Was there an appropriate interval between index test and reference standard?**

Yes

**Did all patients receive the same reference standard?**

Yes

**Were all patients included in the analysis?**

Yes

**Could the patient flow have introduced bias?**

Low risk

### NOTES

Results are not split for oesophageal cancer and gastric cancer.

---

**Stellon (1997)**

### PATIENT SELECTION

**A. risk of bias**

**Patient sampling**

Prospective? consecutive patient series from semi-rural UK general practice with a patient list between 2400-3400 during the study period.

**Was a consecutive or random sample of patients enrolled?**

Yes

**Was a case-control design avoided?**

Yes

**Did the study avoid inappropriate exclusions?**

Yes

**Could the selection of patients have introduced bias?**

Low risk

**B. Concerns regarding applicability**

**Patient characteristics and setting**

N = 26; 5 males, 21 females; age range = 51-87 years.

**Inclusion criteria:** All patients aged > 50 years found to have iron deficiency anaemia between January 1989 and March 1994.

**Exclusion criteria:** None listed.

**Clinical setting:** UK GP

**Are there concerns that the included patients and setting do not match the review question?**

Low concern

### INDEX TEST

**A. Risk of bias**

**Index test**

Iron deficiency anaemia (< 12 g/dl haemoglobin and/or mean corpuscular volume < 80 fl with ferritin ≤ 16 ng/l)

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern
**REFERENCE STANDARD**

### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up during 5 year study period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**


**PATIENT SELECTION**

### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Propective patient series from a group of 49 family physician practices in Canada.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1040, 520 males / 520 females; mean (range) age =45.6 (18-84) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients ≥ 18 years with a primary complaint of ≥ 3 months intermittent or continuous dyspepsia. Patients could not have used proton pump inhibitors within 30 days or prokinetics or prescription H₂-receptor antagonists (H₂RAS) within 14 days of enrolment. Exclusion criteria: Heartburn or acid regurgitation as their sole symptom; documented history of upper GI pathology/surgery; clinical investigation of dyspepsia by endoscopy or radiology in the previous 6 months or more than twice in the past 10 years; H. pylori eradication treatment in the previous 6 months; irritable bowel syndrome as assessed by the presence of ≥ manning criteria; or severe concurrent disease. Clinical setting: Family physician practice, Canada.</td>
<td></td>
</tr>
</tbody>
</table>
Are there concerns that the included patients and setting do not match the review question? | Unclear concern
---|---
**INDEX TEST**
A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia defined as symptom complex of epigastric pain/discomfort in association with other upper GI symptoms, including heartburn and acid regurgitation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 10 days and 6-months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for. 1100/1171 enrolled patients consented to endoscopy, but 60/1100 did not received endoscopy (eligibility criteria not fulfilled [27], lost to follow up [3], withdrew consent [9], non-compliant with the protocol [1], endoscopy-intolerable [2], other [18]).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Malignancy was detected in 2 patients: Gastric (MALToma; 1), oesophageal cancer (1).

Tosetti (2010)

**PATIENT SELECTION**

A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 63 general practitioners in Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting                                    | N = 275; 124 males, 151 females; median age (range) = 46 (18-92) years. Symptoms: Epigastric pain (72%), prolonged digestion (51.6%), heartburn (49.1%), epigastric postprandial fullness (45.5%), epigastric distension (41.5%), nausea (38.5%), acid regurgitation (34.5%), belching (28.7%), early satiety (20.7%). Inclusion criteria: “Each GP enrolled in the survey patients who, over a three-month period, presented with UGI [upper gastro-intestinal] symptoms at the first onset without alarming features.” Exclusion criteria: “Patients with either previous or recurrent complaints or previously investigated for UGI symptoms were not included”. Clinical setting: GPs in Italy |
| Are there concerns that the included patients and setting do not match the review question? | High concern |

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>New onset UGI symptoms without alarming features. Not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | High concern |

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>1-year follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? Low risk

**NOTES**
Cancers diagnosed in these patients were: Pancreas (1/275), and oesophageal (1/275).

Vakil (2009)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling

Prospective patient series

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes (probably)

Could the selection of patients have introduced bias? Unclear risk

**B. Concerns regarding applicability**

Patient characteristics and setting

N = 2741, mean (range) age = not reported (not reported) years, numbers of females/males: Not reported.

Inclusion criteria: Patients aged 18-70 years who met Rome II criteria for dyspepsia (intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months).

Exclusion criteria: Past diagnosis of gastro-oesophageal reflux disease, predominant symptom of heartburn or regurgitation, history of heartburn or regurgitation > 2 days/week, treatment > 2 days/week with non-steroidal anti-inflammatory drugs or cyclooxygenase-2 selective inhibitors or aspirin (except for cardiovascular prophylaxis at doses ≤ 325 mg/day), concurrent alarm features (e.g., dysphagia, recurrent vomiting, unexplained anaemia, gastro-intestinal bleeding), H pylori eradication treatment within 12 months, maintenance therapy with either a proton pump or an H2-receptor antagonist within 6 months.

Clinical setting: The study was conducted in 190 primary care health centers in 17 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Iceland, Italy, Norway, Romania, Singapore, South Africa, Spain, Sweden, Switzerland). Patients were recruited from primary care clinics where flyers publicising the study were placed and the primary care physicians recruited patients presenting to their offices with dyspepsia [random or consecutive sampling unlikely].

Are there concerns that the included patients and setting do not match the review question? Low concern

**INDEX TEST**

**A. Risk of bias**

Index test

Dyspepsia/ intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months. Symptoms were evaluated using a scale validated in a number of languages

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

**B. Concerns regarding applicability**
**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**  
Low concern

**REFERENCE STANDARD**

<table>
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<tr>
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<tr>
<td><strong>Reference standard(s)</strong></td>
<td>All patients received outpatient endoscopy</td>
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<td>Yes</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>No (but all patients had a positive index test)</td>
</tr>
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<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
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**B. Concerns regarding applicability**

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<tr>
<td><strong>Are there concerns that the target condition as defined by the reference standard does not match the question?</strong></td>
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**FLOW AND TIMING**

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<tr>
<td><strong>Flow and timing</strong></td>
<td>All the patients are accounted for in the results.</td>
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<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Yes (probably)</td>
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<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td>Yes</td>
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<tr>
<td><strong>Were all patients included in the analysis?</strong></td>
<td>Yes</td>
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<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
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**NOTES**

Supported by AstraZeneca R&D Sweden. The authors state that “The sponsor did not play any role in the calculations or in the writing of the manuscript”. Six patients had cancer: 3 oesophagus and 3 stomach.


**PATIENT SELECTION**

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<tr>
<td><strong>Patient sampling</strong></td>
<td>Retrospective database study using the laboratory databases of two district general hospitals including all the general practices using these laboratories.</td>
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<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
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<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
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<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
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<td><strong>Could the selection of patients have introduced bias?</strong></td>
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**B. Concerns regarding applicability**

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<tr>
<td><strong>Patient characteristics and setting</strong></td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> All female patients aged &gt; 50 years and male patients aged &gt; 20, with haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10¹²/l between June 1997 and May 1998.</td>
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<tr>
<td><strong>Exclusion criteria:</strong> History of anaemia within previous 12 months, known...</td>
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Suspected Cancer: Appendix F (June 2015)

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<th>INDEX TEST</th>
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<td><strong>Index test</strong></td>
<td>Iron deficiency anaemia (haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10¹²/l)</td>
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<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
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<td><strong>B. Concerns regarding applicability</strong></td>
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<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
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<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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<td>In total N = 48 had gastrointestinal cancer (11 upper, 2 small bowel and 35 lower, including recurrent tumours) and N = 23 had non-gastrointestinal cancers, but the study only reports the type of some of these cancers (3 lung + 1 lung tumour secondary to a previous breast tumour, 1 ovary, 2 bladder, 1 Hodgkin’s, 1 Non-Hodgkin’s, 1 endometrial sarcoma, 1 lymphoma, 1 endometrial) and has therefore not been added to the evidence reviews for the non-gastrointestinal cancers. The paper considers both the lower gastrointestinal cancers and the small bowel cancers as colorectal cancer and in order to present subgroup analyses by gender I have maintained this grouping and not added this paper to the evidence review for small intestine.</td>
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Included studies


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Not in PICO
Not in PICO
Not in PICO

Narrative review


Guideline


Not in PICO


Narrative Review


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Same data as Heikkinen (1995), which is included.
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Narrative review


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Paper on NICE Dyspepsia guideline


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Guideline


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Narrative Review


Same data as Meineche-Schmidt (2002)


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Narrative review
Seifert, B., Vojtiskova, J., Charvatova, E. & Koudelka, T. (2006) Management of gastroesophageal reflux disease (GERD) in primary care. [Czech]. Ceska a Slovenska Gastroenterologie a Hepatologie, 60. Not in PICO (only 3593/9759 registered patients followed up > 12 months, and only 1724 had endoscopy; outcome unclear)


Smith, G. (1936) Red flags are key to managing dyspepsia. [Review] [8 refs]. Practitioner, 251: 31-34. Narrative review


Not in PICO


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Narrative Review


Narrative Review


Narrative review


Narrative review


Not in PICO


Narrative Review


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Narrative Review


In Russian. Not enough information can be extracted to ascertain relevance.


Narrative review


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Narrative Review

Most populations of included studies not in PICO, have checked for relevant papers which will be included separately.

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Narrative Review

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Editorial material

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Included in the Oesophageal tests papers to order

Narrative Review

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Narrative review


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Review question:
Which investigations of symptoms of suspected oesophageal cancer should be done with clinical responsibility retained by primary care?

Results

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Total References retrieved (after de-duplication): 25
Study results
No evidence was identified pertaining to the diagnostic accuracy of upper gastrointestinal endoscopy, barium swallow or chest x-ray in patients with suspected oesophageal cancer where the clinical responsibility was retained by primary care.

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Included studies
None

Excluded studies (with excl reason)
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  Not in PICO
  Not in PICO
  Not in PICO


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Narrative Review


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Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Narrative review


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Narrative review


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Narrative review


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Guideline

Voutilainen, M., Mantynen, T., Maaranen, K., Kunnamo, I. & Juhola, M. (2005) Is it possible to reduce endoscopy workload using age, alarm symptoms and H-pylori as predictors of peptic ulcer and...
Not in PICO

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Narrative Review

In Chinese. Not enough information can be extracted to ascertain relevance.

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Narrative review

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Narrative review
**PANCREATIC CANCER**

**Review question:**
What is the risk of pancreatic cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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<td>2</td>
<td>20/08/2014</td>
</tr>
<tr>
<td>Premedline</td>
<td>5/2013-20/08/2014</td>
<td>90</td>
<td>4</td>
<td>20/08/2014</td>
</tr>
<tr>
<td>Embase</td>
<td>5/2013-20/08/2014</td>
<td>151</td>
<td>11</td>
<td>20/08/2014</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>5/2013-20/08/2014</td>
<td>60</td>
<td>0</td>
<td>20/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>5/2013-20/08/2014</td>
<td>55</td>
<td>2</td>
<td>20/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 17
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and applicability concerns to note in terms of patient selection were that this was not clearly consecutive or random in four of the studies, with three of these studies conducted in a setting that is not clearly directly representative of UK-based primary care. The other bias and applicability concerns to note include missing data, population with restricted age range, short follow up and underspecified presenting symptoms. These issues should all be born in mind when evaluating the evidence.
### Study results

#### Table 1: Pancreatic cancer: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.14 (0.12-0.15) 354/254704</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.1 (0.09-0.12) 154/148290</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>0.19 (0.16-0.22) 200/106768</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.3 (0.3-0.4) 311/94103</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.2 (0.19-0.22) 1540/3635 Cases: 1540/3635 Controls: 1004/16459</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain (attended ≥ twice)</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain</td>
<td>Patients ≥ 60 years</td>
<td>1 (0.8-1.2)</td>
</tr>
<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.23 (0.09-0.53) 6/2585</td>
</tr>
<tr>
<td>Mahadeva (2008)</td>
<td>Dyspepsia</td>
<td>All patients (they were aged 18-45 years)</td>
<td>0.23 (0.01-1.49) 1/432</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Abdominal distension</td>
<td>All patients</td>
<td>0.3 (0.1-0.5) 9/3456</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Abdominal distension</td>
<td>Women</td>
<td>0.16 (0.07-0.34) 7/4457</td>
</tr>
<tr>
<td>Muris (1995)</td>
<td>Non-acute abdominal complaints</td>
<td>All patients</td>
<td>0.21 (0.04-0.86) 2/933</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Dysphagia</td>
<td>All patients</td>
<td>0.2 (0.1-0.4) 11/5442</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Dysphagia</td>
<td>Men</td>
<td>0.1 (0.05-0.19) 9/9326</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>0.39 (0.26-0.59) 24/6078</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.32 (0.17-0.59) 11/3433</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>0.49 (0.27-0.86) 13/2645</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>0.8 (0.5-1.2) 27/3382</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.28 (0.22-0.35) 82/29382</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.16 (0.11-0.24) 26/15954</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>0.42 (0.32-0.54) 56/13428</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.6 (0.5-0.8) 61/9415</td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Group</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------</td>
<td>------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.44</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Weight loss</td>
<td>Patients ≥ 60 years</td>
<td>0.8</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Nausea/vomiting</td>
<td>All patients</td>
<td>0.19</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>0.3</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain</td>
<td>All patients</td>
<td>0.06</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Constipation</td>
<td>All patients</td>
<td>0.1</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Constipation</td>
<td>Males</td>
<td>0.21</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea</td>
<td>All patients</td>
<td>0.09</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Malaise</td>
<td>All patients</td>
<td>0.12</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.2</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice</td>
<td>All patients</td>
<td>12.9</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice</td>
<td>Patients ≥ 60 years</td>
<td>21.6</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>New-onset diabetes</td>
<td>All patients</td>
<td>0.09</td>
</tr>
<tr>
<td>Tosetti (2010)</td>
<td>Upper gastro-intestinal symptoms without alarming features</td>
<td>All patients</td>
<td>0.36</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abnormal liver function</td>
<td>All patients</td>
<td>0.16</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Low haemoglobin</td>
<td>All patients</td>
<td>0.1</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Raised inflammatory</td>
<td>All patients</td>
<td>0.16</td>
</tr>
</tbody>
</table>
The authors report that in patients ≥ 70 years the PPVs for most symptoms were 1.5–4.5 times higher than in patients < 70 years.

Stapley (2012) calculated the positive predictive values using Bayesian statistics. Meta-analyses are not undertaken as the Stapley data cannot be included due to the case-control design of the study. NR = not reported.

Table 2: Pancreatic cancer: Symptom combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and back pain</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and constipation</td>
<td>Patients ≥ 60 years</td>
<td>0.5 (0.4-0.7)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and diarrhoea</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and loss of weight</td>
<td>Patients ≥ 60 years</td>
<td>2.5 (1.5-4.4)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Abdominal pain and jaundice</td>
<td>Patients ≥ 60 years</td>
<td>15 (NR)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and constipation</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.6)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and diarrhoea</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and loss of weight</td>
<td>Patients ≥ 60 years</td>
<td>2 (1-4.3)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Back pain and jaundice</td>
<td>Patients ≥ 60 years</td>
<td>8.9 (NR)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and constipation</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and loss of weight</td>
<td>Patients ≥ 60 years</td>
<td>2.7 (NR)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Diarrhoea and jaundice</td>
<td>Patients ≥ 60 years</td>
<td>&gt; 10*</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Constipation and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Nausea/vomiting and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.5 (0.3-0.8)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------</td>
<td>---------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Constipation and weight loss</td>
<td>Patients ≥ 60 years</td>
<td>1.5 (0.8-3)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Constipation and nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Nausea/vomiting and weight loss</td>
<td>Patients ≥ 60 years</td>
<td>2.2 (1.1-4.6)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Weight loss and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>1.6 (1-2.9)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>New onset diabetes and jaundice</td>
<td>Patients ≥ 60 years</td>
<td>22.3 (NR)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Constipation and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.3-0.6)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Malaise and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.5 (0.3-0.9)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Nausea/vomiting and new onset diabetes</td>
<td>Patients ≥ 60 years</td>
<td>0.7 (0.5-1)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Weight loss and malaise</td>
<td>Patients ≥ 60 years</td>
<td>0.9 (0.4-2.1)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice and nausea/vomiting</td>
<td>Patients ≥ 60 years</td>
<td>14.6 (NR)</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice and constipation</td>
<td>Patients ≥ 60 years</td>
<td>&gt;10*</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice and malaise</td>
<td>Patients ≥ 60 years</td>
<td>&gt;10*</td>
</tr>
<tr>
<td>Stapley (2012)</td>
<td>Jaundice and weight loss</td>
<td>Patients ≥ 60 years</td>
<td>&gt;10*</td>
</tr>
</tbody>
</table>

Stapley (2012) calculated the positive predictive values using Bayesian statistics. NR = not reported.

* > 40 cases and 0 controls had these symptoms.

**Evidence statement(s):**

For pancreatic cancer the positive predictive values of single symptoms (7 studies, N = 3146347) presenting in primary care ranged from 0.06% (for back pain) to 21.6% (for jaundice). The included studies were associated with 0-4 bias/applicability concerns (see also Table 1).

For pancreatic cancer the positive predictive values of symptom combinations (1 study, N = 20094) presenting in primary care ranged from 0.2% (for diarrhoea in combination with either constipation, nausea/vomiting or back pain) to 22.3% (for new onset diabetes combined with jaundice). The included study was associated with 1 bias concern (see also Table 2).

**Evidence tables**

**Collins (2013)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>A total of 2150322 patients were identified from 364 practices. <strong>Symptoms:</strong> Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326). <strong>Incident cases of pancreatic cancer during the 2-year follow up period:</strong> N = 618 (331 men, 287 women). <strong>Inclusion criteria:</strong> Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. <strong>Exclusion criteria:</strong> Patients with a prior diagnosis of pancreatic cancer, registration &lt; 12 months with the general practice, or invalid dates. <strong>Clinical setting:</strong> Primary care, UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>‘Red-flag’ symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

**A. risk of bias**

<p>| Flow and timing | All patients seem to be accounted for |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Hallissey (1990)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling: Prospective consecutive patient series from a group of 10 general practices in England.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Patient characteristics and setting: N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.

<table>
<thead>
<tr>
<th>Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria: None listed.</td>
</tr>
<tr>
<td>Clinical setting: Primary care, England.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

**INDEX TEST**

**A. Risk of bias**

Index test: Dyspepsia of any degree

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

Reference standard(s): Upper gastrointestinal endoscopy within 4 weeks and follow up.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?  Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing  2659 patients were seen and 2585 attended for investigation

Was there an appropriate interval between index test and reference standard?  Yes

Did all patients receive the same reference standard?  Yes

Were all patients included in the analysis?  Yes

Could the patient flow have introduced bias?  Low risk

NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).

Hippisley-Cox (2012)

PATIENT SELECTION

A. risk of bias

Patient sampling  Prospective patient series using patients in the QResearch database (version 30).

Was a consecutive or random sample of patients enrolled?  Yes

Was a case-control design avoided?  Yes

Did the study avoid inappropriate exclusions?  Yes

Could the selection of patients have introduced bias?  Low risk

B. Concerns regarding applicability

Patient characteristics and setting  A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recoded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172). Incident cases of pancreatic cancer during the 2-year follow up period: N = 781.

Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from
patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>A total of 1342329 patients were initially identified of whom 98589 patients...</td>
</tr>
</tbody>
</table>
were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | No |
| Could the patient flow have introduced bias? | High risk |

**NOTES**

Mahadeva (2008)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling

Prospective patient series from the Primary Care Clinics of the University of Malaya in Malaysia

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

Could the selection of patients have introduced bias? Unclear risk

**B. Concerns regarding applicability**

Patient characteristics and setting

N = 432; 198 males/234 females; mean ages (SDs) = 30-31 (8) years.

Inclusion criteria: “All patients were recruited from the Primary Care Clinics of the University of Malaya, which provide a regular service to the local community. Patients aged ≤ 45 years presenting with uninvestigated dyspepsia were invited to participate in the study”, which ran from January 2004 until October 2005.

Exclusion criteria: Age > 45 or < 18 years; symptoms of weight loss, progressive dysphagia or those suggestive of anaemia; pregnancy; previous H pylori testing; any contra-indication to endoscopy or sedation; failure to turn up for initial test ; and on regular doses of non-steroidal anti-inflammatory drugs.

Clinical setting: Primary care clinic, Malaysia

Are there concerns that the included patients and setting do not match the review question? High concern

**INDEX TEST**

**A. Risk of bias**

Index test

Uninvestigated dyspepsia. Dyspepsia defined as predominant upper abdominal discomfort for > 4 weeks, with any associated symptoms, including heart burn and regurgitation.

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk
### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up ± upper endoscopy (oesophagogastroduodenoscopy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>39/471 eligible patients were excluded from the study for the following reasons: 34/39 patients declined to participate, 3/39 became pregnant before the test, 1/39 emigrated from the country and 1/39 had missing data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### NOTES

One patient was found to have cancer, which was metastatic pancreatic cancer. No oesophageal or gastric cancers were reported.

---

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 80/460 general practitioners in Limburg (Holland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 933; 335 males, 598 females; age range = 18-75, aged &gt; 30 years: N = 712, aged &gt; 40 years: N = 517, aged &gt; 60 years: N = 171.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
</tbody>
</table>
### Clinical setting: GPs in Holland

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>High concern</th>
</tr>
</thead>
</table>

### INDEX TEST

<table>
<thead>
<tr>
<th>Index test</th>
<th>New abdominal complaints lasting ≥ 2 weeks. Not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### INDEX TEST

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>High concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up for ≥ 12 months (mean = 18 months).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

| Cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), kidney (1/933), colorectal (4/933), cervix (1/933), other cancer of the female genital system (2/933), and other and unspecified sites (2/933). |

### Stapley (2012)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the</td>
<td>Yes</td>
</tr>
<tr>
<td>comparison groups for potential confounders?</td>
<td></td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding</td>
<td>Yes</td>
</tr>
<tr>
<td>and prognostic factors?</td>
<td></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>High risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

#### Patient characteristics and setting

<table>
<thead>
<tr>
<th>Cases:</th>
<th>Controls:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 3635, 1743 males / 1892 females; median number of consultations = 18</td>
<td>N = 16459, gender not reported; median number of consultations = 9 (IQR = 4-15);</td>
</tr>
<tr>
<td>(IQR = 11-27); aged 40-49 years: N = 107; 50-59 years: N = 529; 60-69 years:</td>
<td>aged 40-49 years: N = 422; 50-59 years: N = 2239; 60-69 years: N = 3755; 70-79</td>
</tr>
<tr>
<td>N = 829; 70-79 years: N = 1212; ≥ 80 years: N = 958; UK.</td>
<td>years: N = 5702; ≥ 80 years: N = 4341; UK.</td>
</tr>
</tbody>
</table>

**Inclusion criteria:**
- Cases: Patients with a record of one of 25 GPRD pancreatic cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a pancreatic cancer code was assigned the data of diagnosis/index date.
- Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.
- **Exclusion criteria:** Pancreatic cancer (controls), no consultations in the year before diagnosis.
- **Clinical setting:** Primary care

#### Are there concerns that the included patients and setting do not match the review question?

| Low concern |

### INDEX TEST

#### A. Risk of bias

**Index test**

All symptoms, physical signs or abnormal investigations compiled from the pancreatic cancer literature were studied, and supplemented by discussion with two pancreatic cancer charities. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. Repeat attendances with the same symptom were also retained if the subsequent consultation also occurred in ≥5% of cases or controls. New-onset diabetes was defined as a code for diabetes, or a random blood glucose above the local laboratory’s normal range, without similar codes more than 1 year before the index date. For laboratory tests, patients without a test were considered to be the same status as those with a normal result, making our binary variable abnormal result/ no abnormal result. Abnormal liver function was defined as any liver enzyme above the normal range, and raised inflammatory markers as either abnormal erythrocyte sedimentation rate or
**C-reactive protein, as there were too few plasma viscosity results.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Pancreatic cancer code in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>A total of 21624 patients were identified, 17977 controls and 3647 cases. Of the controls the following exclusions were applied: pancreatic cancer (N = 64), case excluded (N = 40), and no data in year pre-index date (N = 1414). Of the cases the following exclusions were applied: No controls (N = 2), and cancer not of pancreatic origin (N = 10).</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Tosetti (2010)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series from 63 general practitioners in Italy</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>High risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

| Patient characteristics and setting | N = 275; 124 males, 151 females; median age (range) = 46 (18-92) years. Symptoms: Epigastric pain (72%), prolonged digestion (51.6%), heartburn (49.1%), epigastric postprandial fullness (45.5%), epigastric distension (41.5%), nausea (38.5%), acid regurgitation (34.5%), belching (28.7%), early satiety (20.7%).
| Inclusion criteria: “Each GP enrolled in the survey patients who, over a three-month period, presented with UGI [upper gastro-intestinal] symptoms at the first onset without alarming features.”
| Exclusion criteria: “Patients with either previous or recurrent complaints or previously investigated for UGI symptoms were not included”. 
| Clinical setting: GPs in Italy |

**Are there concerns that the included patients and setting do not match the review question?**

| High concern |

**INDEX TEST**

| A. Risk of bias |

| Index test | New onset UGI symptoms without alarming features. Not further specified. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | High concern |

**REFERENCE STANDARD**

| A. Risk of bias |

| Reference standard(s) | 1-year follow up. |
| Is the reference standard likely to correctly classify the target condition? | Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

| A. Risk of bias |

| Flow and timing | All patients appear to be accounted for |
| Was there an appropriate interval between index test and reference standard? | Unclear |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| Could the patient flow have introduced bias? | Low risk |

**NOTES**

| Cancers diagnosed in these patients were: Pancreas (1/275), and |
References

Included studies


Excluded studies (with reason)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Evans, J., Chapple, A., Salisbury, H., Corrie, P. & Ziebland, S. (2014) "It can't be very important because it comes and goes"-patients' accounts of intermittent symptoms preceding a pancreatic cancer diagnosis: a qualitative study. *Bmj Open*, 4.
Not in PICO


Not in PICO

Not in PICO

Narrative review

Narrative review


Narrative review

Not in PICO

Narrative review

Duplicate

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO (does not present PPVs)

Data in Hippisley-Cox 2012 on pancreatic cancer

Not in PICO

Not in PICO

Not in PICO

Same as Homma 1991

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

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**Review question:**

Which investigations of symptoms of suspected pancreatic cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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Total References retrieved (after de-duplication): 33
Study results

No evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, MRI, CEA, Beta hCG or tumour markers CA19-9 and CA72-4 in patients with suspected pancreatic cancer where the clinical responsibility was retained by primary care.

References

Included studies

Excluded studies (with excl reason)


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European experts consensus statement on cystic tumours of the pancreas. *Digestive & Liver Disease, 45*: 703-711.

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and Hepatology, 8: 629-634.
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Suspected Cancer: Appendix F (June 2015)
Nuclear Medicine Communications, 26: 895-901.
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Narrative review


Narrative review
STOMACH CANCER

Review question:
What is the risk of stomach cancer in patients presenting in primary care with symptom(s)?

Results

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Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in a setting that may not directly translate to UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity. The evidence base is also limited by the fact that some of the positive predictive value estimates are based on low numbers of patients and a number of the studies do not provide different estimates for stomach and oesophageal cancer, but only provide one estimate for these cancers combined.
Study results

Table 1: Stomach cancer: Meta-analyses

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Legend:
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- Yellow (?): Unclear
- Green (+): Low
Please note that the data from Stapley (2013) are not included in these meta-analyses due to the case-control design of the study, and the data from Mahadeva (1998) is not included due to the limited and different age range of the population. These data are instead reported in the table below entitled “Additional results reported by the individual papers: Single symptoms“. When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead.

Table 2: Stomach cancer: Individual positive predictive values from the meta-analyses

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<th>Patient group</th>
<th>PPVs % (95% CI); prevalence</th>
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<td>Dyspepsia</td>
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<td>All patients</td>
<td>1.04 (0.27-3.28)</td>
</tr>
<tr>
<td>Farrus Palou (2000)</td>
<td>Anaemia</td>
<td>All patients</td>
<td>1.7 (0.09-10.5)</td>
</tr>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Anaemia</td>
<td>All patients</td>
<td>1.1 (1-1.4)</td>
</tr>
<tr>
<td>Stellon (1997)</td>
<td>Anaemia</td>
<td>All patients</td>
<td>0 (0-0)</td>
</tr>
</tbody>
</table>
### Table 3: Stomach cancer: Additional results reported by the individual papers: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tosetti (2010)</td>
<td>Upper gastro-intestinal symptoms without alarming features</td>
<td>All patients</td>
<td>0 (0-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/275</td>
</tr>
<tr>
<td>Muris (1993)</td>
<td>Non-acute abdominal complaints</td>
<td>All patients</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/578</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Abdominal pain</td>
<td>Women</td>
<td>0.1 (0.1-0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>139/144266</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>0.3 (0.3-0.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>298/102732</td>
</tr>
</tbody>
</table>

### Table: Suspected Cancer: Additional results reported by the individual papers

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yates (2004)</td>
<td>Anaemia</td>
<td>All patients</td>
<td>2.55 (1.35-4.66)</td>
</tr>
<tr>
<td>Brignoli (1997)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.4 (0.09-1.14)</td>
</tr>
<tr>
<td>Duggan (2008)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.27 (0.05-1.1)</td>
</tr>
<tr>
<td>Edenholm (1985)</td>
<td>Persistent epigastric pain/ulcer-like dyspepsia</td>
<td>All patients</td>
<td>1.2 (0.21-4.77)</td>
</tr>
<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>2.28 (1.76-3)</td>
</tr>
<tr>
<td>Hansen (1998)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>1 (0.4-2.2)</td>
</tr>
<tr>
<td>Heikkinen (1995)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>1.75 (0.8-3.7)</td>
</tr>
<tr>
<td>Jaskiewicz (1991)</td>
<td>Dyspepsia</td>
<td>All included patients</td>
<td>2.7 (1.6-4.5)</td>
</tr>
<tr>
<td>Kagevi (1989)</td>
<td>Dyspepsia</td>
<td>All included patients</td>
<td>1.16 (0.2-4.6)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.54 (0.25-1.1)</td>
</tr>
<tr>
<td>Thomson (2003)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.1 (0.01-0.6)</td>
</tr>
<tr>
<td>Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>All included patients</td>
<td>0.1 (0.03-0.35)</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Dysphagia</td>
<td>All patients</td>
<td>4.2 (3.9-4.5)</td>
</tr>
<tr>
<td>Esfandyari (2002)</td>
<td>Dysphagia</td>
<td>All patients</td>
<td>6 (2.5-13.1)</td>
</tr>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Dysphagia</td>
<td>All patients</td>
<td>7.8 (7.1-8.5)</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Dysphagia</td>
<td>All patients</td>
<td>0.78 (0.58-1.05)</td>
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</tbody>
</table>

Tosetti (2010) reported: Upper gastro-intestinal symptoms without alarming features. 11/431 has UGI cancer: No distinction made between the different kinds.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Condition</th>
<th>Population</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>0.3 (0.2-0.3)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.8-1)</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Anaemia</td>
<td>Women</td>
<td>0.4 (0.3-0.5)</td>
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<td></td>
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<td>49/13792</td>
</tr>
<tr>
<td></td>
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<td>Men</td>
<td>1.5 (1.1-1.9)</td>
</tr>
<tr>
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<td>67/4563</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Anaemia</td>
<td>Men</td>
<td>0 (0-44)</td>
</tr>
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</tr>
<tr>
<td>Stapley (2013)</td>
<td>Low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.2 (0.2-109)</td>
</tr>
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<td>Jaskiewicz (1991)</td>
<td>Dyspepsia</td>
<td>Males</td>
<td>3.4 (1.8-6)</td>
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</tr>
<tr>
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<td></td>
<td>Females</td>
<td>1.7 (0.6-4.7)</td>
</tr>
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</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.6-0.7)</td>
</tr>
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<td>Stapley (2013)</td>
<td>Dyspepsia (reported ≥ twice)</td>
<td>Patients ≥ 55 years</td>
<td>1.2 (1-1.5)</td>
</tr>
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<td>Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>Patients ≥ 45 years old</td>
<td>0.27 (0.07-0.84)</td>
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<td>Patients ≥ 50 years old</td>
<td>0.36 (0.09-1.15)</td>
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<td>Patients ≥ 55 years old</td>
<td>0 (0-0.86)</td>
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<td>Patients ≥ 60 years old</td>
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<td>Reflux-like dyspepsia</td>
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<td>Unclassifiable dyspepsia</td>
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<td>0.9 (0.05-5.8)</td>
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<td>1/107</td>
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<td>Mahadeva (2008)</td>
<td>Dyspepsia</td>
<td>All patients (aged 18-45 years)</td>
<td>0 (0-1.1)</td>
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<td>Dysphagia</td>
<td>Women</td>
<td>2.5 (2.2-2.8)</td>
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<td>262/10391</td>
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<td>Men</td>
<td>6.2 (5.7-6.7)</td>
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<td>548/8846</td>
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<tr>
<td>Jones (2007)</td>
<td>Dysphagia</td>
<td>Women</td>
<td>0.5 (0.3-0.8)</td>
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<td>17/3371</td>
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<td>Men</td>
<td>1.14 (0.79-1.65)</td>
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<tr>
<td>Stapley (2013)</td>
<td>Dysphagia</td>
<td>Patients ≥ 55 years</td>
<td>4.8 (4.3-5.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia (reported ≥ twice)</td>
<td>Patients ≥ 55 years</td>
<td>5.5 (4.2-7.9)</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
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<td>37/5838</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.4 (0.2-0.7)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>12/3317</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>1 (0.7-1.5)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptom(s)</td>
<td>Patient group</td>
<td>Positive predictive value, % (95% CI)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------------</td>
<td>---------------</td>
<td>-------------------------------------</td>
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<tr>
<td>Hippisley-Cox (2011)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>1.1 (0.8-1.5) 35/3391</td>
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<tr>
<td>Møllmann (1981)</td>
<td>Weight loss and/or anorexia</td>
<td>All patients</td>
<td>2 (0.1-12) 1/50</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.8 (0.7-0.9) 218/28403</td>
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<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.6 (0.4-0.7) 86/15465</td>
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<td></td>
<td></td>
<td>Men</td>
<td>1 (0.9-1.2) 132/12938</td>
</tr>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>1.2 (1-1.4) 107/9170</td>
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<td>Stapley (2013)</td>
<td>Weight loss</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1)</td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Haematemesis</td>
<td>All patients</td>
<td>1 (0.8-1.2) 110/10792</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.5 (0.3-0.7) 22/4630</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>1.4 (1.2-1.8) 88/6162</td>
</tr>
<tr>
<td>Hippisley-Cox (2011)</td>
<td>Haematemesis</td>
<td>All patients</td>
<td>2.3 (1.9-2.7) 101/4477</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation</td>
<td>Patients ≥ 55 years</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.6-0.7)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Nausea and/or vomiting &gt; 2 weeks</td>
<td>All patients</td>
<td>0 (0-12.3) 0/35</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.5-0.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting reported ≥ twice</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.5 (0.4-0.5)</td>
</tr>
</tbody>
</table>

Stapley (2013) reported that all PPVs for symptom combinations in patients < 55 years were < 1%, and that the highest PPV in this age group was for dysphagia, 0.8 (0.4-1.5)%

Møllmann (1981) reported that all PPVs for symptom combinations in patients < 55 years were < 1%

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and jaundice</td>
<td>All patients</td>
<td>0 (0-48.32) 0/6</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and black stools</td>
<td>All patients</td>
<td>0.91 (0.05-5.69) 1/110</td>
</tr>
<tr>
<td>Meineche-Schmidt</td>
<td>Dyspepsia and bloody</td>
<td>All patients</td>
<td>0.76 (0.04-4.81)</td>
</tr>
<tr>
<td>Year</td>
<td>Conditions</td>
<td>Age Group</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>(2002)</td>
<td>Stools</td>
<td></td>
<td>1/131</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>5.8 (3.5-10.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>9.2 (4.4-22.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>6.5 (3.5-13.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>9.3 (NR)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and reflux</td>
<td>Patients ≥ 55 years</td>
<td>5 (3.3-8.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>4.6 (3.4-6.6)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>7.3 (4.4-13.9)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and dysphagia</td>
<td>All patients</td>
<td>1.4 (0.04-4.36)</td>
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<td>Stapley (2013)</td>
<td>Dysphagia and dyspepsia</td>
<td>Patients ≥ 55 years</td>
<td>9.8 (5.7-20.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dysphagia and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>6.1 (3.2-13.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and abdominal pain</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.7-1.3)</td>
</tr>
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<td>Stapley (2013)</td>
<td>Dyspepsia and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (1-2)</td>
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<tr>
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<td>Dyspepsia and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>1.3 (0.9-1.8)</td>
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<td>Stapley (2013)</td>
<td>Dyspepsia and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and weight loss</td>
<td>All patients</td>
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</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>2.1 (1.3-3.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and anaemia</td>
<td>All patients</td>
<td>0 (0-11.71)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Dyspepsia and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.3)</td>
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<tr>
<td>Stapley (2013)</td>
<td>Constipation and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.4 (0.3-0.5)</td>
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<td>Stapley (2013)</td>
<td>Constipation and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>1.1 (0.8-1.7)</td>
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<td>Patients ≥ 55 years</td>
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<td>Constipation and epigastric pain</td>
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<td>0.7 (0.5-1.1)</td>
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<td>Group</td>
<td>Odds Ratio (CI)</td>
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<td>--------------------</td>
<td>--------------------------------------------------</td>
<td>----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.4 (0.4-0.5)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.4-0.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and dyspepsia</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and dysphagia</td>
<td>Patients ≥ 55 years</td>
<td>4.2 (2.7-7.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Constipation and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and chest pain</td>
<td>Patients ≥ 55 years</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (0.9-2.2)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea/vomiting &gt; 2 weeks</td>
<td>All patients</td>
<td>0.7 (0.12-2.7) 2/293</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.7 (0.5-0.9)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.5 (0.4-0.6)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Abdominal pain and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-21) 0/19</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea/vomiting &gt; 2 weeks and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-44) 0/7</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and nausea/vomiting &gt; 2 weeks and weight loss/anorexia</td>
<td>All patients</td>
<td>5.2 (2.1-11.4) 6/116</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and weight loss/anorexia and gastrointestinal bleeding</td>
<td>All patients</td>
<td>20 (1.1-70) 1/5</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks and weight loss/anorexia</td>
<td>All patients</td>
<td>2 (0.4-7.9) 2/98</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and reflux</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.5-0.9)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptom Combination</td>
<td>Population</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and nausea/vomiting</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.4-0.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Chest pain and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.8 (0.6-1.2)</td>
</tr>
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<td>Stapley (2013)</td>
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<td>Patients ≥ 55 years</td>
<td>1.5 (1-2.4)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>4.2 (1.8-11)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Epigastric pain and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1.6 (1.1-2.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux and loss of weight</td>
<td>Patients ≥ 55 years</td>
<td>3.1 (1.5-6.7)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Reflux and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>0.9 (0.7-1.2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Weight loss and low haemoglobin</td>
<td>Patients ≥ 55 years</td>
<td>1 (0.8-1.3)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia and gastrointestinal bleeding</td>
<td>All patients</td>
<td>0 (0-80) 0/2</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia and gastrointestinal bleeding and nausea/vomiting &gt; 2 week</td>
<td>All patients</td>
<td>0 (0-80) 0/2</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Weight loss/anorexia and nausea/vomiting &gt; 2 week</td>
<td>All patients</td>
<td>0 (0-16.6) 0/25</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and weight loss</td>
<td>Patients ≥ 55 years</td>
<td>2.8 (1.7-4.8)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and epigastric pain</td>
<td>Patients ≥ 55 years</td>
<td>1.3 (0.9-2)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and reflux</td>
<td>Patients ≥ 55 years</td>
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<tr>
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<tr>
<td>Stapley (2013)</td>
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<tr>
<td>Stapley (2013)</td>
<td>Nausea/vomiting and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>1.4 (1-2.1)</td>
</tr>
<tr>
<td>Stapley (2013)</td>
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<td>Patients ≥ 55 years</td>
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</tr>
<tr>
<td>Stapley (2013)</td>
<td>Low haemoglobin and raised platelets</td>
<td>Patients ≥ 55 years</td>
<td>0.6 (0.6-0.7)</td>
</tr>
<tr>
<td>Møllmann (1981)</td>
<td>Any of the inclusion symptoms + previous dyspepsia</td>
<td>All patients</td>
<td>0.9 (0.4-1.9) 7/773</td>
</tr>
</tbody>
</table>
Møllmann (1981)  Any of the inclusion symptoms + no previous dyspepsia  All patients  2.1 (1.1-3.8)  11/524

Møllmann (1981)  Any of the inclusion symptoms + unchanged previous dyspepsia  All patients  1.2 (0.5-3)  5/407

Møllmann (1981)  Any of the inclusion symptoms + no previous or changed dyspepsia  All patients  1.5 (0.8-2.6)  13/890

Møllmann (1981)  Any of the inclusion symptoms + pain provoked by meals  All patients  2.3 (1-5.3)  6/257

Møllmann (1981)  Any of the inclusion symptoms + no pain provoked by meals  All patients  1.1 (0.6-2.1)  10/924

Møllmann (1981)  Any of the inclusion symptoms + relief of pain by meals  All patients  1.2 (0.5-2.8)  6/488

Møllmann (1981)  Any of the inclusion symptoms + no pain relief by meals  All patients  1.5 (0.7-2.8)  10/687

Møllmann (1981)  Any of the inclusion symptoms + irritable bowel syndrome  All patients  1.2 (0.2-4.7)  2/167

Møllmann (1981)  Any of the inclusion symptoms + no irritable bowel syndrome  All patients  1.4 (0.8-2.3)  16/1129

Please note:
- The calculations of the positive predictive values differ between the all the other included studies using (TP)/(TP+FP) and Stapley (2013) using other statistics due to the case-control design of these studies. NR = not reported.

Evidence statement(s):

Abdominal pain (4 studies, N = 3416339) presenting in a primary care setting is associated with an overall positive predictive value of up to 0.34% for stomach cancer. The studies were associated with 0-3 bias or applicability concerns (see also Tables 1-3).

Anaemia (8 studies, N = 3417170) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.09% for stomach cancer. The studies were associated with 0-4 bias or applicability concerns (see also Tables 1-3).

Dyspepsia (13 studies, N = 52183) presenting in a primary care setting is associated with an overall positive predictive value of up to 1.2% for stomach cancer. The studies were associated with 1-3 bias or applicability concerns (see also Tables 1-3).

Dysphagia (5 studies, N = 4177284) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.5% for stomach cancer. All the studies were associated with 0-1 bias or applicability concerns (see also Tables 1-3).
Other single symptoms (6 studies, N = 3417192) presenting in a primary care setting are associated with an overall positive predictive values for stomach cancer up to 2.3% (for haematemesis). The studies were associated with 0-4 bias or applicability concerns (see also Table 3).

Two or more symptom presenting in combination (3 studies, N = 43319) in a primary care setting are associated with overall positive predictive values for stomach cancer ranging from 0% (dyspepsia with jaundice or anaemia, for ‘gastrointestinal bleeding and nausea/vomiting and upper abdominal pain’, and for ‘gastrointestinal bleeding and anorexia/weightloss’ with or without nausea/vomiting) to 20% (for ‘upper abdominal pain and weight loss/anorexia and gastrointestinal bleeding’), but some of these positive predictive values were based on very low numbers of patients. The studies were associated with 1-3 bias or applicability concerns (see also Table 4).

Evidence tables

Brignoli (1997)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: “Adult patients with epigastric complaints were admitted to the multicentre [omega]-project if their symptoms persisted for over 1 month and their clinical history and appearance did not suggest an organic disorder (i.e. absence of alarm features, such as gastrointestinal blood loss, palpable tumour mass, massive weight loss, etc.). The studies were conducted by general practitioners acting as primary care physicians.”</td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
</tr>
<tr>
<td>Clinical setting: Primary care, Switzerland</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
</tbody>
</table>

INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
</tbody>
</table>

REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>standard(s)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

|  | **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Flow and timing</th>
<th>All patients are accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Were all patients included in the analysis?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

3 patients had gastric cancer, 0 patients had oesophageal cancer, and 2 patients had cancer outside the digestive tract.

**Collins (2012)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women). Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. |
### Exclusion criteria
Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates.

### Clinical setting
Primary care, UK

### Are there concerns that the included patients and setting do not match the review question?
Low concern

### INDEX TEST

#### A. Risk of bias

**Index test**
‘Red-flag’ symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.

- **Were the index test results interpreted without knowledge of the results of the reference standard?** Yes
- **Could the conduct or interpretation of the index test have introduced bias?** Low risk

#### B. Concerns regarding applicability

- **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

#### A. Risk of bias

- **Reference standard(s)**
2-year follow up
- **Is the reference standard likely to correctly classify the target condition?** Yes
- **Were the reference standard results interpreted without knowledge of the results of the index tests?** Unclear
- **Could the reference standard, its conduct, or its interpretation have introduced bias?** Low risk

#### B. Concerns regarding applicability

- **Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

### FLOW AND TIMING

#### A. Risk of bias

- **Flow and timing**
All patients seem to be accounted for
- **Was there an appropriate interval between index test and reference standard?** Yes
- **Did all patients receive the same reference standard?** Yes
- **Were all patients included in the analysis?** Yes
- **Could the patient flow have introduced bias?** Low risk

### NOTES

Droogendijk (2011)

### PATIENT SELECTION

#### A. Risk of bias

- **Patient sampling**
Retrospective peripheral hospital laboratory database study serving 265 GPs in Dordrecht (Holland).
- **Was a consecutive or random sample of patients enrolled?** Yes
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 287; 129 men, 158 women; median (range) age = 70 (19-87) years.</td>
</tr>
<tr>
<td>Inclusion criteria: All women aged &gt; 50 years and all men aged ≥ 18 years who between January 2004 and December 2005 were diagnosed with iron-deficiency anaemia (haemoglobin &lt; 13.7 g/dl in men and &lt; 12.1 g/dl in women, and a serum ferritin level &lt; 25 µg/l for men and &lt; 20 µg/l for women).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with a known history of iron-deficiency anaemia in the previous 2 years, a history of gastrointestinal malignancy or congenital haemoglobinopathy.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Holland</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>New onset iron-deficiency anaemia (haemoglobin &lt; 13.7 g/dl in men and &lt; 12.1 g/dl in women, and a serum ferritin level &lt; 25 µg/l for men and &lt; 20 µg/l for women).</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Endoscopy and 12-month follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>It is unclear if all patients are accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>NOTES</td>
<td>In addition to the 24 patients with colorectal cancer, 3 patients had gastric cancer, 1 patient had oesophageal cancer and 1 patient had locally invasive endometrial cancer.</td>
</tr>
</tbody>
</table>

Duggan (2008)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling | Prospective patient series from 43 GP practices in the UK.

Was a consecutive or random sample of patients enrolled? | No

Was a case-control design avoided? | Yes

Did the study avoid inappropriate exclusions? | Yes

**Could the selection of patients have introduced bias?** | Unclear risk

**B. Concerns regarding applicability**

**Patient characteristics and setting** | N = 762; 411 men, 351 women; mean (range) age = 42 (18-73) years.

Inclusion criteria: Patients aged 18-70 with dyspepsia thought by the GP to arise from the upper GI tract and of sufficient severity to justify empirical treatment with an H₂ antagonist or PPI.

Exclusion criteria: Patients thought to be unfit for investigation, with alarm symptoms suggestive of malignancy (dysphagia, weight loss > 5 g, anaemia, haematemesis, melena or jaundice), previous radiological or endoscopic diagnosis of peptic ulcer disease or reflux oesophagitis, investigation for dyspepsia in the previous 5 years with either procedure or symptom onset within 6 months of commencement of NSAID therapy, previous H. pylori eradication therapy or more than 3 prescriptions for acid suppression therapy in the previous 6 months.

Clinical setting: Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?** | Low concern

**INDEX TEST**

**A. Risk of bias**

**Index test** | Dyspepsia

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes

**Could the conduct or interpretation of the index test have introduced bias?** | Low risk

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern

**REFERENCE STANDARD**

**A. risk of bias**

**Reference standard(s)** | Endoscopy and 1-2-year follow up.

**Is the reference standard likely to correctly classify the** | Yes
<table>
<thead>
<tr>
<th><strong>target condition?</strong></th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>At 12-month follow up GP data were available for 753/762.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>2 patients had gastric cancer, 2 patients had oesophageal cancer (the authors report that these patients should not have been included as they had a history of dysphagia).</td>
</tr>
</tbody>
</table>

**Edenholm (1985)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th><strong>A. risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series from the Distric General Clinic in Huskvarna, Sweden.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 187; 96 men, 91 women; mean/median (range) age = 44 (17-80) years.</td>
</tr>
<tr>
<td>Inclusion criteria: Patients who between November 1982 and June 1984 called on the clinic because of abdominal pain and who were diagnosed by the general practitioner as having ulcer-like dyspepsia. The criterion used was persistent epigastric pain. Most patients also had additional symptoms such as acid regurgitation, nausea, belching or vomiting.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Sweden</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

**INDEX TEST**

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Ulcer-like dyspepsia. The criterion used was persistent epigastric pain.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Could the conduct or interpretation of the index test have introduced bias? | Low risk
---|---

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**REFERENCE STANDARD**

**A. risk of bias**

| Reference standard(s) | UGI endoscopy |
---|---

Is the reference standard likely to correctly classify the target condition? | Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? | No

Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern

**FLOW AND TIMING**

**A. risk of bias**

| Flow and timing | 20/187 patients declined endoscopy and it was unsuccessful in a further 2 patients. Thus the PPV is likely to be an over-estimate, calculated as 2/165.
---|---

Was there an appropriate interval between index test and reference standard? | Yes probably

Did all patients receive the same reference standard? | Yes

Were all patients included in the analysis? | No

Could the patient flow have introduced bias? | High risk

**NOTES**

There were a total of 3 cancers confirmed in the 165 patients who received UGI endoscopy: 1 oesophageal cancer, 1 stomach cancer, and 1 cancer of the duodenum, the latter of which was included with the stomach cancer

Esfandyari (2002)

**PATIENT SELECTION**

**A. risk of bias**

| Patient sampling | Prospective/retrospective? patient series from USA |
---|---

Was a consecutive or random sample of patients enrolled? | Yes

Was a case-control design avoided? | Yes

Did the study avoid inappropriate exclusions? | Yes

Could the selection of patients have introduced bias? | Low risk

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 100; 49 men, 51 women; mean (SE) age = 64 (2) years. |
---|---

Inclusion criteria: Patients with new onset dysphagia without a prior work up who were evaluated at the Cleveland Clinic Foundation outpatient clinic by their primary care physician.

Exclusion criteria: Neurological disease, oropharyngeal dysphagia or previous
gastric or oesophageal surgery, and patients without a final diagnosis explaining their dysphagia.
Clinical setting: Primary care outpatient clinic, USA.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>High concern</th>
</tr>
</thead>
</table>

## INDEX TEST
### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>New onset dysphagia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

## REFERENCE STANDARD
### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Completed clinical and diagnostic testing after an initial barium swallow/upper GI endoscopy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

## FLOW AND TIMING
### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

## NOTES

6 patients had malignancy, but the type of malignancy was not further specified

Farrus Palou (2000)

## PATIENT SELECTION
### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective consecutive patient series from urban general practice covering a population of 24000.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Did the study avoid inappropriate exclusions?
Yes

### Could the selection of patients have introduced bias?
Low risk

### B. Concerns regarding applicability

**Patient characteristics and setting**

N = 87 of whom the data from 29 were unavailable as no etiological diagnosis was found (due to patient refusal of further investigation [?; 8], lost to follow up [7], patient deterioration rendering them unsuitable for further investigation [14]); of the remaining 58 patients there were 14 males, 44 females; mean? (SD?) age = 54.26 (19.95) years.

**Inclusion criteria:** Patients aged > 14 years who attended the health centre between 1 October 1995 and 31 September 1996 who were found to have new onset (previously unknown) anaemia (haemoglobin < 13 g/dl for men and 12 g/dl for women).

**Exclusion criteria:** Pregnant women.

**Clinical setting:** Spanish GP

### Are there concerns that the included patients and setting do not match the review question?
Unclear concern

### INDEX TEST

#### A. Risk of bias

**Index test**

Anaemia (haemoglobin < 13 g/dl for men and 12 g/dl for women)

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**

Follow up I think

**Is the reference standard likely to correctly classify the target condition?**

Unclear

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

No

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

Unclear risk

#### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

Unclear concern

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**

No diagnosis available for 29/87 patients

**Was there an appropriate interval between index test and reference standard?**

Unclear

**Did all patients receive the same reference standard?**

Yes

**Were all patients included in the analysis?**

No
| **Could the patient flow have introduced bias?** | High risk |
| **NOTES** | This paper is published in Spanish. One patient had gastric cancer, 2 patients had colon cancer. |

**Hallissey (1990)**

**PATIENT SELECTION**

**A. risk of bias**

| Patient sampling | Propective consecutive patient series from a group of 10 general practices in England. |
| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| **Could the selection of patients have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia. |
| Inclusion criteria | All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia |
| Exclusion criteria | None listed. |
| Clinical setting | Primary care, England. |
| **Are there concerns that the included patients and setting do not match the review question?** | Unclear concern |

**INDEX TEST**

**A. Risk of bias**

| Index test | Dyspepsia of any degree |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

| Reference standard(s) | Upper gastrointestinal endoscopy within 4 weeks and follow up. |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |
FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

Patient characteristics and setting

N = 612 from 66 GPs; 288 males / 324 females; mean age (SD) = 47 (16.8) years.

Inclusion criteria: “All general practitioners (n = 108) in the city of Odense (population, 170,000) were invited to participate in the study. GPs were asked to refer all patients who consulted them with dyspepsia, regardless of the severity of the symptoms. To obtain compliance with this request the participating GPs were sent numerous reminders. Because of a limited endoscopy capacity not all GPs took part in the study at the same time.” Study period was 11 March 1991-27 March 1992.

Exclusion criteria: Aged < 18 years, signs of UGI bleeding, abdominal emergency, jaundice, previous surgery in the UGI tract except for closure of an ulcer, supposed acute bacterial or viral infection, pregnancy, or endoscopy contraindicated.

Clinical setting: GPs in Denmark

Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge</td>
</tr>
<tr>
<td>A. risk of bias</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
</tr>
<tr>
<td>A. risk of bias</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
</tbody>
</table>

**NOTES**

There were a total of 4 cancers histologically confirmed in the study. No subclassification of the cancers reported. Follow up of the 364 patients with normal endoscopy revealed missing date in 5% of the cases and 1 lymphoma and 1 rectal carcinoma. These 6 cancers (NOS) are included in the overall PPV for dyspepsia.

Heikkinen (1995)

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Consecutive patient series from 11 GPs (from 3 rural health centres) and from the catchment area of 6 physicians in the health centre of an urban area (population [individuals &gt; 14 years old] of study area = 24600) in Finland.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 400; 152 males, 248 females; 77% were &gt; 44 years.</td>
</tr>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP from January 11th 1993 to January 12th 1994 for dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with symptoms of an acute condition within the abdomen or who had had an upper intestinal endoscopy performed within the last 3 months or aged &lt; 15 years</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, Finland.</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td>INDEX TEST</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or its interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Upper gastrointestinal endoscopy, upper abdominal ultrasound, more detailed interview, blood count, serum screening (creatinine, alkaline phosphatase, alanine aminotransferase, amylase, and C-reactive protein), lactose intolerance test, and follow up of ≥ 1 month.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and</td>
<td>Yes</td>
</tr>
<tr>
<td>reference standard?</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

In total N = 9 had cancer: 0 colorectal, 2 oesophageal and 7 stomach (of which 3 were lymphomas of the MALT type (Mucosa-associated lymphoid tissue).

**Hippisley-Cox (2011)**

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling: Prospective patient series using patients in the QResearch database (version 30).

| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| Could the selection of patients have introduced bias? | Low risk |

**B. Concerns regarding applicability**

Patient characteristics and setting:

A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6).

**Symptoms:**

Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638), haemoglobin < 11 g/dl in the last year (N = 218862).

Incident cases of colorectal cancer during the 2-year follow up period: N = 1343 (776 oesophageal and 567 gastric).

**Inclusion criteria:**

All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.*

**Exclusion criteria:** Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

**Clinical setting:** Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?** | Low concern |
### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>‘Red-flag’ symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.</td>
</tr>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</strong></td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference standard(s)</strong></td>
<td>2-year follow up</td>
</tr>
<tr>
<td><strong>Is the reference standard likely to correctly classify the target condition?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
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</table>

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<thead>
<tr>
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<th></th>
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<tbody>
<tr>
<td><strong>Are there concerns that the target condition as defined by the reference standard does not match the question?</strong></td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow and timing</strong></td>
<td>A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</td>
</tr>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Were all patients included in the analysis?</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### NOTES

- Results not presented separately for gastric and oesophageal cancer

### Jaskiewicz (1991)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient sampling</strong></td>
<td>Patient series from a program aimed at screening patients with chronic gastric complaints for gastric carcinoma in the South and North-Western Cape Province of South Africa.</td>
</tr>
</tbody>
</table>
## Was a consecutive or random sample of patients enrolled?

**Unclear**

## Was a case-control design avoided?

**Yes**

## Did the study avoid inappropriate exclusions?

**Unclear**

## Could the selection of patients have introduced bias?

**Unclear risk**

### B. Concerns regarding applicability

#### Patient characteristics and setting

N = 585, 355 males, 230 females; mean (range) age males = 45.1 (19-87) years, mean (range) age females = 47.2 (19-87) years.

Inclusion criteria: “participants who were treated for dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months. Patients represented various areas in the south-and north-western Cape province including Namaqualand, and formed part of a programme aimed at screening patients with chronic gastric complaints for gastric carcinoma.”

Exclusion criteria: None listed

**Clinical setting:** Unclear, South Africa.

#### Are there concerns that the included patients and setting do not match the review question?

**Unclear concern**

### INDEX TEST

#### A. Risk of bias

#### Index test

Unspecified dyspepsia (dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months).

**Were the index test results interpreted without knowledge of the results of the reference standard?**

**Yes**

**Could the conduct or interpretation of the index test have introduced bias?**

**Low risk**

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

**Unclear concern**

### REFERENCE STANDARD

#### A. Risk of bias

#### Reference standard(s)

Endoscopy

**Is the reference standard likely to correctly classify the target condition?**

**Yes**

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

**No**

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

**Low risk**

#### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

**Low concern**

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**

All patients appear to be accounted for

**Was there an appropriate interval between index test and**

**Yes**
<table>
<thead>
<tr>
<th>reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES
In total N = 16 had gastric cancer. No oesophageal cancers reported

Jones (2007)

PATIENT SELECTION

A. risk of bias

Patient sampling
Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.

Was a consecutive or random sample of patients enrolled? | Yes |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Could the selection of patients have introduced bias? | Low risk |

B. Concerns regarding applicability

Patient characteristics and setting
A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years.

Number of first occurrences in patients with no previous diagnosis of cancer:

- **Haematuria**: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years.
- **Haemoptysis**: N = 4822, mean (SD) age at first symptom = 61.6 (18) years.
- **Dysphagia**: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years.
- **Rectal bleeding**: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years.

Patients excluded due to incomplete dates for their first symptom:

- **Haematuria**: N = 30. Sex (of final sample): 6385 males, 4723 females.
- **Haemoptysis**: N = 10. Sex (of final sample): 2930 males, 1882 females.
- **Dysphagia**: N = 4. Sex (of final sample): 2628 males, 3371 females.

Inclusion criteria: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.

Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.

Clinical setting: Primary care

Are there concerns that the included patients and setting do not match the review question? | Low concern |

INDEX TEST
### A. Risk of bias

#### Index test
- Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

#### B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

### REFERENCE STANDARD

#### A. Risk of bias
- Reference standard(s): Cancer code in the UK’s General Practice Research Database:
  - Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs.
  - Haemoptysis: Respiratory tract neoplasms.
  - Dysphagia: Oesophageal neoplasms.
  - Rectal bleeding: Colorectal neoplasms.

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear (but all patients had a positive index test)

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

#### B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

### FLOW AND TIMING

#### A. Risk of bias
- Flow and timing: All patients are accounted for in the results.

Was there an appropriate interval between index test and reference standard? Unclear

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Low risk

#### NOTES
- Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates. Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:
  - Haematuria: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.
**Dysphagia:** Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women [reported in the paper, however, the numbers reported do not match up and I think the PPV is instead 2.91%; 98/3371] and 6.9% in men. 

*Estimates based on the pre-specified cancers may be thus conservative for these symptoms.*

**Haemoptysis:** Extension of the diagnostic criteria yielded 6 additional cancers.

**Rectal bleeding:** Extension of the diagnostic criteria yielded 2 additional cancers.

---

### Kagevi (1989)

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th><strong>A. risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient sampling</strong></td>
<td>Propective consecutive patient series from a primary care centre in Sweden.</td>
</tr>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

**Patient characteristics and setting**

N = 172; 88 men, 84 women; mean (SD) age = 43 (16) years.

**Inclusion criteria:** “All patients visiting the medical center with complaints referable to the digestive tract were considered for inclusion. Even when the patient consulted the primary care center because of another complaint and coincidentally mentioned gastrointestinal problem, the patient was considered for inclusion. The patient’s gastrointestinal problem could have been reported in connection with an earlier visit at the primary care center.”

**Exclusion criteria:** Patients with jaundice, gastrointestinal bleeding or acute abdominal pain were excluded and so were patients judged to have a non-gastro-enterologic cause of their symptoms (gynaecologic problems, spondylosis deformans, etc), patients aged < 16 years and patients unwilling to participate.

**Clinical setting:** Primary care Center, Sweden.

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

#### INDEX TEST

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>Dyspepsia defined as any pain, discomfort, or other symptoms referable to the digestive tract ≥ 2 weeks. Symptoms could be intermittent or continuous.</td>
</tr>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern
REFERENCE STANDARD

A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Esophagogastroduodenoscopy within 1 week and 6 month follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>13/185 patients were excluded as they did not want to have an endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

2 patients had gastric cancer, 0 patients had oesophageal cancer.

Mahadeva (2008)

PATIENT SELECTION

A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from the Primary Care Clinics of the University of Malaya in Malaysia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 432; 198 males/234 females; mean ages (SDs) = 30-31 (8) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: “All patients were recruited from the Primary Care Clinics of the University of Malaya, which provide a regular service to the local community. Patients aged ≤ 45 years presenting with uninvestigated dyspepsia were invited to participate in the study”, which ran from January 2004 until October 2005.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Age &gt; 45 or &lt; 18 years; symptoms of weight loss, progressive dysphagia or those suggestive of anaemia; pregnancy; previous H pylori testing; any contra-indication to to endoscopy or sedation; failure to turn up for initial test ; and on regular doses of non-steroidal anti-inflammatory drugs.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care clinic, Malaysia</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>High concern</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>Uninvestigated dyspepsia. Dyspepsia defined as predominant upper abdominal discomfort for &gt; 4 weeks, with any associated symptoms, including heart burn and regurgitation.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up ± upper endoscopy (oesophagastroduodenoscopy)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>39/471 eligible patients were excluded from the study for the following reasons: 34/39 patients declined to participate, 3/39 became pregnant before the test, 1/39 emigrated from the country and 1/39 had missing data.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>One patient was found to have cancer, which was metastatic pancreatic cancer. No oesophageal or gastric cancers were reported.</td>
</tr>
</tbody>
</table>

Meineche-Schmidt (2002)

**PATIENT SELECTION**

<p>| <strong>A. Risk of bias</strong> | |
| Patient sampling | Consecutive patient series from 82 GPs in Denmark. |
| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |</p>
<table>
<thead>
<tr>
<th>Did the study avoid inappropriate exclusions?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1491; 688 males, 803 females; age groups: 18-37 years: N = 377; 38-50 years: N = 369; 51-64 years: N = 338; 65- years: N = 402.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP between June 1991 and May 1993 for dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, Denmark.</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>18 months-3 years and 10 months follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

In total N = 31 had cancer: 17 colorectal, 8 gastro-oesophageal (no subgroup analyses presented for these patients) and 6 other.
### Muris (1993)

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive patient series from 11 general practitioners in Maastricht (Holland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>N = 578; 212 males, 342 females; age groups: 18-39 years: N = 295; 40-49 years: N = 80; 50-59 years: N = 91; 60-75 years: N = 88.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients who during a 3-month period consulted one of the participating GPs for abdominal complaints.</td>
</tr>
<tr>
<td>Exclusion criteria: Patients aged &lt; 18 years and patients with a condition necessitating immediate referral or admission to hospital.</td>
</tr>
<tr>
<td>Clinical setting: GPs in Holland</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

#### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Abdominal complaints. Not further specified, but the authors do report that the duration of pain before the patient presented for the first time for the evaluation of abdominal pain varied from some days to more than 1 year.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Unclear concern |

#### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up for 15 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

#### FLOW AND TIMING
## A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td><strong>Unclear</strong></td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### NOTES
Although not explicitly stated by the authors it is implied that the patients included were those presenting with the abdominal complaint for the first time.

---

### Møllmann (1981)

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

- **Patient characteristics and setting**
  - N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years N = 47; 90-99 years: N = 8.
  - **Inclusion criteria:** All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).
  - **Exclusion criteria:** Patients who had been examined for any of the above symptoms within the last 6 months.
  - **Clinical setting:** GPs in Denmark

- Are there concerns that the included patients and setting do not match the review question? | **Unclear concern**

#### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

- Are there concerns that the index test, its conduct, or interpretation differ from the review question? | **Low concern**

#### REFERENCE STANDARD

| A. risk of bias |
### Reference standard(s)

2-stage process: Gastroscopy with photography, using a gastrocamera, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Did the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

### FLOW AND TIMING

#### A. risk of bias

Flow and timing: 177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes probably</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Did the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported. This research was published in 2 papers.

### Stapley (2013)

### PATIENT SELECTION

#### A. risk of bias

Patient sampling: Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

- Attempts were made within the design or analysis to balance the comparison groups for potential confounders? Yes
- The groups were comparable at baseline, including all major confounding and prognostic factors? Yes

**Could the selection of patients have introduced bias?**

<table>
<thead>
<tr>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Characteristic and setting</th>
<th>Cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal cancer cases:</td>
<td>N = 4854, 3174 males / 1680 females; aged 40-54 years: N = 387; 55-69</td>
</tr>
</tbody>
</table>
years: N = 1712; 70-84 years: N = 2230; ≥ 85 years: N = 532.
Gastric cancer cases:
N = 2617, 1625 males / 992 females; aged 40-54 years: N = 130; 55-69 years: N = 671; 70-84 years: N = 1437; ≥ 85 years: N = 382.
Median number of consultations (all cases) = 26 (IQR = 15-42)
Controls:
Oesophageal cancer controls:
N = 21506, gender not reported; aged 40-54 years: N = 1539; 55-69 years: N = 7473; 70-84 years: N = 10296; ≥ 85 years: N = 2198.
Gastric cancer controls:
N = 11371, gender not reported; aged 40-54 years: N = 497; 55-69 years: N = 2887; 70-84 years: N = 6431; ≥ 85 years: N = 1556.
Median number of consultations (all controls) = 15 (IQR = 7-28)

Inclusion criteria:
Cases: Patients with a record of one of 42 (18 oesophageal, 24 gastric) GPRD tumour diagnostic codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of an oesophago-gastric cancer code was assigned the data of diagnosis/index date.
Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.
Exclusion criteria: Oesophago-gastric cancer (controls), no consultations in the year before diagnosis.
Clinical setting: Primary care, UK

Are there concerns that the included patients and setting do not match the review question? Low concern

INDEX TEST

A. Risk of bias

Index test

All symptoms, physical signs or abnormal investigations compiled from the oesophago-gastric cancer literature were studied, and supplemented by literature from relevant cancer websites. The GPRD’s code list has many synonyms for for similar symptoms, often including additional description such as severity or duration. These synonyms were identified and merged. The dyspepsia variable merged codes with either the word ‘dyspepsia’ or ‘indigestion’; the reflux variable included ‘regurgitation’ as well as ‘reflux’; the variable ‘epigastric pain’ required a precise anatomical description, whereas the variable ‘abdominal pain’ incorporated all other abdominal pain variables without a precise anatomical description. Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. For laboratory tests, the local laboratory range was used to identify abnormal results. Patients without a test were considered to be the same status as those with a normal result. All hepatic enzyme results were merged into a composite variable, deemed abnormal if any enzyme was raised; similarly, abnormal erythrocyte sedimentation rate, plasma viscosity and C-reactive protein were collated into a single variable called raised inflammatory markers. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal).
### Were the index test results interpreted without knowledge of the results of the reference standard?
- Yes

### For diagnostic case-control studies:
- Investigators were kept 'blind' to other important confounding and prognostic factors?
- Yes

### Could the conduct or interpretation of the index test have introduced bias?
- Low risk

### B. Concerns regarding applicability
- Are there concerns that the index test, its conduct, or interpretation differ from the review question?
- Low concern

### REFERENCE STANDARD

#### A. risk of bias
- **Reference standard(s):** Oesophago-gastric cancer code in the UK’s General Practice Research Database.
- Is the reference standard likely to correctly classify the target condition?
- Yes
- Were the reference standard results interpreted without knowledge of the results of the index tests?
- Unclear
- Could the reference standard, its conduct, or its interpretation have introduced bias?
- Low risk

#### B. Concerns regarding applicability
- Are there concerns that the target condition as defined by the reference standard does not match the question?
- Low concern

### FLOW AND TIMING

#### A. risk of bias
- Flow and timing:
  - A total of 45356 patients were identified, 37699 controls and 7657 cases. Of the controls the following exclusions were applied: Already used as a case (N = 252), case excluded (N = 808), duplicate control (N = 427) and no data in year pre-index date (N = 3335). Of the cases the following exclusions were applied: No controls (N = 17), OG cancer diagnosis before 2000 (N = 28), case already used as case (for other O/G cancer: N = 131) and case with metastatic cancer (N = 10).
- Was there an appropriate interval between index test and reference standard?
- Yes
- Did all patients receive the same reference standard?
- Yes
- Were all patients included in the analysis?
- Yes
- Could the patient flow have introduced bias?
- Low risk

### NOTES
- Results are not split for oesophageal cancer and gastric cancer.

### Stellon (1997)

### PATIENT SELECTION

#### A. risk of bias
- Patient sampling:
  - Prospective? consecutive patient series from semi-rural UK general practice with a patient list between 2400-3400 during the study period.
- Was a consecutive or random sample of patients enrolled?
- Yes
- Was a case-control design avoided?
- Yes
### Did the study avoid inappropriate exclusions?
Yes

### Could the selection of patients have introduced bias?
Low risk

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 26; 5 males, 21 females; age range = 51-87 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: All patients aged &gt; 50 years found to have iron deficiency anaemia between January 1989 and March 1994.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: UK GP</td>
<td></td>
</tr>
</tbody>
</table>

### Are there concerns that the included patients and setting do not match the review question?
Low concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Iron deficiency anaemia (&lt; 12 g/dl haemoglobin and/or mean corpuscular volume &lt; 80 fl with ferritin ≤ 16 ng/l)</th>
</tr>
</thead>
</table>

### Could the conduct or interpretation of the index test have introduced bias?
Low risk

### B. Concerns regarding applicability

### Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low concern

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up during 5 year study period.</th>
</tr>
</thead>
</table>

### Could the reference standard, its conduct, or its interpretation have introduced bias?
Low risk

### B. Concerns regarding applicability

### Are there concerns that the target condition as defined by the reference standard does not match the question?
Low concern

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
</table>

### Could the patient flow have introduced bias?
Low risk

### NOTES

## PATIENT SELECTION
### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Propective patient series from a group of 49 family physician practices in Canada.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1040, 520 males / 520 females; mean (range) age =45.6 (18-84) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients ≥ 18 years with a primary complaint of ≥ 3 months intermittent or continuous dyspepsia. Patients could not have used proton pump inhibitors within 30 days or prokinetics or prescription H₂-receptor antagonists (H₂RAS) within 14 days of enrolment.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Heartburn or acid regurgitation as their sole symptom; documented history of upper GI pathology/surgery; clinical investigation of dyspepsia by endoscopy or radiology in the previous 6 months or more than twice in the past 10 years; H. pylori eradication treatment in the previous 6 months; irritable bowel syndrome as assessed by the presence of ≥ manning criteria; or severe concurrent disease.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Family physician practice, Canada.</td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia defined as symptom complex of epigastric pain/discomfort in association with other upper GI symptoms, including heartburn and acid regurgitation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 10 days and 6-months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<p>| | |
| | |</p>
<table>
<thead>
<tr>
<th><strong>Are there concerns that the target condition as defined by the reference standard does not match the question?</strong></th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for. 1100/1171 enrolled patients consented to endoscopy, but 60/1100 did not received endoscopy (eligibility criteria not fulfilled [27], lost to follow up [3], withdrew consent [9], non-compliant with the protocol [1], endoscopy-intolerable [2], other [18]).</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>COULD THE PATIENT FLOW HAVE INTRODUCED BIAS?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Malignancy was detected in 2 patients: Gastric (MALToma; 1), oesophageal cancer (1).</td>
</tr>
</tbody>
</table>

**Tosetti (2010)**

| **PATIENT SELECTION** |  |
| **A. risk of bias** |  |
| Patient sampling | Prospective patient series from 63 general practitioners in Italy |
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Unclear |
| **COULD THE SELECTION OF PATIENTS HAVE INTRODUCED BIAS?** | High risk |
| **B. Concerns regarding applicability** |  |
| Patient characteristics and setting | N = 275; 124 males, 151 females; median age (range) = 46 (18-92) years. Symptoms: Epigastric pain (72%), prolonged digestion (51.6%), heartburn (49.1%), epigastric postprandial fullness (45.5%), epigastric distension (41.5%), nausea (38.5%), acid regurgitation (34.5%), belching (28.7%), early satiety (20.7%). |
| Inclusion criteria: “Each GP enrolled in the survey patients who, over a three-month period, presented with UGI [upper gastro-intestinal] symptoms at the first onset without alarming features.” |
| Exclusion criteria: “Patients with either previous or recurrent complaints or previously investigated for UGI symptoms were not included”. |
| Clinical setting: GPs in Italy |
| **Are there concerns that the included patients and setting do not match the review question?** | High concern |
| **INDEX TEST** |  |
| **A. Risk of bias** |  |
| Index test | New onset UGI symptoms without alarming features. Not further specified. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| **COULD THE CONDUCT OR INTERPRETATION OF THE INDEX TEST HAVE INTRODUCED BIAS?** | Low risk |
| **B. Concerns regarding applicability** |  |
Are there concerns that the index test, its conduct, or interpretation differ from the review question? | High concern

REFERENCE STANDARD

A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>1-year follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

Cancers diagnosed in these patients were: Pancreas (1/275), and oesophageal (1/275).

Vakil (2009)

PATIENT SELECTION

A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 2741, mean (range) age = not reported (not reported) years, numbers of females/males: Not reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients aged 18-70 years who met Rome II criteria for dyspepsia (intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Past diagnosis of gastro-oesophageal reflux disease, predominant symptom of heartburn or regurgitation, history of heartburn or regurgitation &gt; 2 days/week, treatment &gt; 2 days/week with non-steroidal anti-inflammatory drugs or cycloxygenase-2 selective inhibitors or aspirin (except for cardiovascular prophylaxis at doses ≤ 325 mg/day), concurrent alarm features (e.g., dysphagia, recurrent vomiting, unexplained anaemia,</td>
<td></td>
</tr>
</tbody>
</table>
gastro-intestinal bleeding), H pylori eradication treatment within 12 months, maintenance therapy with either a proton pump or an H2-receptor antagonist within 6 months.

Clinical setting: The study was conducted in 190 primary care health centers in 17 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Iceland, Italy, Norway, Romania, Singapore, South Africa, Spain, Sweden, Switzerland). Patients were recruited from primary care clinics where flyers publicising the study were placed and the primary care physicians recruited patients presenting to their offices with dyspepsia [random or consecutive sampling unlikely].

| Are there concerns that the included patients and setting do not match the review question? | Low concern |
| A. Risk of bias | |
| Index test | Dyspepsia/ intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months. Symptoms were evaluated using a scale validated in a number of languages |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

REFERENCE STANDARD

A. risk of bias

| Reference standard(s) | All patients received outpatient endoscopy |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No (but all patients had a positive index test) |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

A. risk of bias

| Flow and timing | All the patients are accounted for in the results. |
| Was there an appropriate interval between index test and reference standard? | Yes (probably) |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| Could the patient flow have introduced bias? | Low risk |

NOTES

Supported by AstraZeneca R&D Sweden. The authors state that “The sponsor did not play any role in the calculations or in the writing of the manuscript”.

Suspected Cancer: Appendix F (June 2015) Page 348 of 1735
Six patients had cancer: 3 Oesophagus and 3 stomach.


**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Retrospective database study using the laboratory databases of two district general hospitals including all the general practices using these laboratories.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 431; 154 males, 277 females; median age (inter-quartile range) = 75 (65-81) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: All female patients aged &gt; 50 years and male patients aged &gt; 20, with haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10^{12}/l between June 1997 and May 1998.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: History of anaemia within previous 12 months, known haematological abnormalities (e.g., haemoglobinopathy), unavailable notes at follow up. That is, patients with a history of cancer were not excluded. Clinical setting: UK GP</td>
<td></td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Iron deficiency anaemia (haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10^{12}/l)</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Minimum 3 years follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
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<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
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<tr>
<td>Were all patients included in the analysis?</td>
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<tr>
<td>Could the patient flow have introduced bias?</td>
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</table>

### NOTES

In total N = 48 had gastrointestinal cancer (11 upper, 2 small bowel and 35 lower, including recurrent tumours) and N = 23 had non-gastrointestinal cancers, but the study only reports the type of some of these cancers (3 lung + 1 lung tumour secondary to a previous breast tumour, 1 ovary, 2 bladder, 1 Hodgkin's, 1 Non-Hodgkin's, 1 endometrial sarcoma, 1 lymphoma, 1 endometrial) and has therefore not been added to the evidence reviews for the non-gastrointestinal cancers. The paper considers both the lower gastrointestinal cancers and the small bowel cancers as colorectal cancer and in order to present subgroup analyses by gender I have maintained this grouping and not added this paper to the evidence review for small intestine.

### References

**Included studies**


Excluded studies (with excl reason)


Narrative review

Not in PICO

Narrative review

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Suspected Cancer: Appendix F (June 2015)


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Smith, G. (1936) Red flags are key to managing dyspepsia. [Review] [8 refs]. Practitioner, 251: 31-34.
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Review question:
Which investigations of symptoms of suspected stomach cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

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**SSCI) and ISI Proceedings**

Total References retrieved (after de-duplication): 256

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Total References retrieved (after de-duplication): 21

- # of records identified through database searching: N = 277
- # of additional records identified through other sources: N = 0
- # of records screened: N = 277
- # of records excluded: N = 210
- # of full-text articles assessed for eligibility: N = 67
- # of full-text articles excluded, with reasons: N = 67 (Narrative review: N = 9, Not in PICO: N = 55, Not enough information available: N = 1, Comment: N = 1, Duplicate: N = 1)
- # of studies included in qualitative synthesis: N = 0
- # of studies included in quantitative synthesis (meta-analysis): N = 0

### Study results

No evidence was identified pertaining to the diagnostic accuracy of upper gastrointestinal endoscopy, barium meal or abdominal ultrasound in patients with suspected stomach cancer where the clinical responsibility was retained by primary care.

### References

**Included studies**

None
Excluded studies (with excl reason)
Not in PICO
Not in PICO
Not in PICO
Not available, but I think it is not in PICO
Not in PICO
Guideline
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Not in PICO
Narrative review
Not in PICO
Setting is unclear, but don’t think population is in PICO
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Narrative review

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Not in PICO
Clinicopathological findings and histological appearance of early gastric cancer. [Japanese]. 
Not in PICO

_Endoscopy_, 26: 767-768.
Duplicate

Narrative review

Not in PICO

Not in PICO

Smith, G. (1936) Red flags are key to managing dyspepsia. [Review] [8 refs]. _Practitioner_, 251: 31-34.
Narrative review

(1990) [Gastroscopy in follow-up studies of patients with chronic atrophic gastritis and diagnosis 
Not in PICO

Not in PICO

oesophago-gastric cancer in symptomatic patients in primary care: A large case-control study 
Not in PICO

Basic principles, techniques, and clinical experience. _Endoscopy_, 30: 379-386.
Narrative review

and histological analysis of gastric mucosa biopsy in diagnosing malignant diseases]. [Croatian]. 
_Lijecnicki Vjesnik_, 126: 287-290.
Not in PICO

Sturgeon, C. M., Duffy, M. J., Hofmann, B. R., Lamerz, R., Fritsche, H. A., Gaarenstroom, K., Bonfrer, 
laboratory medicine practice guidelines for use of tumor markers in liver, bladder, cervical, and 
Guideline

Not in PICO

upper gastrointestinal endoscopy in India. _Singapore Medical Journal_, 49: 970-976.
Not in PICO

Swaroop, V. S., Mohandas, K. M., Swarooop, V. D., Soman, C. S., Krishnamurthi, S., Nagral, A., 
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Foreign language, not enough information can be extracted to definitely ascertain relevance, but I strongly think it is not in PICO


Unavailable, but I think it is not in PICO


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Narrative review

Narrative review

Comment

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SMALL INTESTINAL CANCER

Review question:
What is the risk of small intestine cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

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Total References retrieved (after de-duplication): 117

Update Search

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Total References retrieved (after de-duplication): 7
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the patient recruitment method is unclear and that the study patients may therefore not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP.

Study results
Table 1: Small intestinal cancer: Study results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>PPVs % (95% CI); prevalence</th>
</tr>
</thead>
</table>
| Vakil (2009)| Dyspepsia without alarm symptoms | All included patients | 0.2 (0.09-0.5) 6/2741 Cancer:
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Dyspepsia without alarm symptoms</th>
<th>Age Group</th>
<th>Cancer Incidence (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 (0.2-1.1) 5/1127</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer:</td>
<td>Oesophagus: N = 2, Stomach: N = 3</td>
</tr>
<tr>
<td>Vakil (2009)</td>
<td>Patients ≥ 50 years old</td>
<td>Oesophagus: N = 2, Stomach: N = 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.6 (0.2-1.5) 5/829</td>
</tr>
<tr>
<td>Vakil (2009)</td>
<td>Patients ≥ 55 years old</td>
<td>Oesophagus: N = 1, Stomach: N = 0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.2 (0.009-1.2) 1/554</td>
</tr>
<tr>
<td>Vakil (2009)</td>
<td>Patients ≥ 60 years old</td>
<td>Oesophagus: N = 1, Stomach: N = 0</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3 (0.02-2) 1/323</td>
</tr>
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</table>

TP = True positives, FP = False positives.

**Evidence statement(s):**

Dyspepsia without accompanying alarm features (1 study, N = 2741) presenting in a primary care setting do not appear to confer an increased risk of small intestine cancer, although the study population is probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

**Evidence tables**

**Vakil (2009)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
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<tbody>
<tr>
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</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
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<th>Patient characteristics and setting</th>
<th>N = 2741, mean (range) age = not reported (not reported) years, numbers of females/males: Not reported.</th>
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</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients aged 18-70 years who met Rome II criteria for dyspepsia (intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months).</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Past diagnosis of gastro-oesophageal reflux disease,</td>
</tr>
</tbody>
</table>
predominant symptom of heartburn or regurgitation, history of heartburn or regurgitation > 2 days/week, treatment > 2 days/week with non-steroidal anti-inflammatory drugs or cyclooxygenase-2 selective inhibitors or aspirin (except for cardiovascular prophylaxis at doses ≤ 325 mg/day), concurrent alarm features (e.g., dysphagia, recurrent vomiting, unexplained anaemia, gastro-intestinal bleeding), H pylori eradication treatment within 12 months, maintenance therapy with either a proton pump or an H2-receptor antagonist within 6 months.

**Clinical setting:** The study was conducted in 190 primary care health centers in 17 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Iceland, Italy, Norway, Romania, Singapore, South Africa, Spain, Sweden, Switzerland). Patients were recruited from primary care clinics where flyers publicising the study were placed and the primary care physicians recruited patients presenting to their offices with dyspepsia [random or consecutive sampling unlikely].

**Are there concerns that the included patients and setting do not match the review question?** Low concern

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia/ intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months. Symptoms were evaluated using a scale validated in a number of languages</th>
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<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
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</table>

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or its interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>All patients received outpatient endoscopy</th>
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<tr>
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<td>Yes</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
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</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the review question? | Low concern |

### FLOW AND TIMING

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for in the results.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Yes (probably)</td>
</tr>
</tbody>
</table>
Did all patients receive the same reference standard? | Yes
---|---
Were all patients included in the analysis? | Yes
Could the patient flow have introduced bias? | Low risk

NOTES

Supported by AstraZeneca R&D Sweden. The authors state that “The sponsor did not play any role in the calculations or in the writing of the manuscript.”

**References**

**Included studies**


**Excluded studies (with excl reason)**


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO

Catena, Fausto, Di Saverio, Salomone, Kelly, Michael, Biffl, Walter, Ansaloni, Luca, Mandala, Vincenzo, Velmabos, George, Sartelli, Massimo, Tognoli, Gregorio, Lupo, Massimo, Mandala,
Excl reason: Guideline

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Excl reason: Narrative review

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Excl reason: Not in PICO
Donohue, J. H. Malignant tumours of the small bowel. [Review] [60 refs]. Surgical Oncology 3[2], 61-68. 1994.
Excl reason: Narrative review

Excl reason: Not in PICO (but include for colorectal)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

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Excl reason: Not in PICO

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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Goh, B. K., Chow, P. K., Kesavan, S. M., Yap, W. M., Chung, Y. F., and Wong, W. K. A single-institution experience with eight CD117-positive primary extragastrointestinal stromal tumors: critical appraisal and a comparison with their gastrointestinal counterparts. Journal of Gastrointestinal
Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

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Kennington, E. How community pharmacists can help in the early detection of bowel cancer. Pharmaceutical Journal 288[7702], 497. 21-4-2012.
Excl reason: Not in PICO

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McMurrick, P., Dorien, S., and Shapiro, J. Bowel cancer - guide for the GP. [Review] [7 refs].
Australian Family Physician 35[4], 192-197. 2006.
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Orlandi, M. and Inauen, W. [Chronic gastrointestinal bleeding]. [Review] [6 refs] [German].

Therapeutische Umschau 63[5], 327-332. 2006.

Excl reason: Narrative review


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Excl reason: Not in PICO


Excl reason: Narrative review

Excl reason: Not in PICO (abstract: Screened population, not split by symptom or cancer)


Excl reason: Not in PICO


Excl reason: Narrative review


Excl reason: Not in PICO


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Excl reason: Not in PICO
Which investigations of symptoms of suspected small intestine cancer should be done with clinical responsibility retained by primary care?

Results

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### Study results

No evidence was identified pertaining to the diagnostic accuracy of CT scan, barium follow through or capsule endoscopy in patients with suspected small intestine cancer where the clinical responsibility was retained by primary care.

### References

**Included studies**

None

**Excluded studies (with excl reason)**


  Not in PICO


  Narrative review


  Not in PICO

Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


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Narrative review

In Korean, not enough information can be extracted, but it appears to be "Not in PICO".

Narrative review

Not in PICO

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Narrative review


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Not in PICO

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Narrative review
Narrative review

Narrative review

Not in PICO

Comment

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Guideline

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Narrative review

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Narrative review

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Not in PICO
delayed diagnosis due to misinterpretation of diagnostic imaging and symptom confusion due to
Not in PICO
**GALL BLADDER CANCER**

**Review question:**
What is the risk of gall bladder cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the patient sample may not be directly applicable to the current question.

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<thead>
<tr>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
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<td>Patient Selection</td>
<td>Hallissey (1990)</td>
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<tr>
<td>Index Test</td>
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<td>Reference Standard</td>
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<td>Flow and Timing</td>
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<td></td>
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Study results

Table 1: Gall bladder cancer: Positive predictive values for gall bladder cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
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<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.04 (0.002-0.3) 1/2585</td>
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Evidence statement(s):

The positive predictive value of having gall bladder cancer was 0.04% (for dyspepsia) for patients aged > 40 years (1 study, N = 2585). The included study was associated with 1 applicability concern (see also Table 1).

Evidence tables

Hallissey (1990)

<table>
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<th>PATIENT SELECTION</th>
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<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
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<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
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<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
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</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
</tr>
<tr>
<td>Clinical setting:</td>
</tr>
<tr>
<td><strong>Are there concerns that the included patients and setting do not match the review question?</strong></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>INDEX TEST</th>
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<tr>
<td><strong>A. Risk of bias</strong></td>
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<tr>
<td>Index test</td>
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<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
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</table>

<table>
<thead>
<tr>
<th>REFERENCE STANDARD</th>
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<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
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<tr>
<td>Reference standard(s)</td>
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<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
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<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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<tr>
<td><strong>Could the reference standard, its conduct, or its</strong></td>
</tr>
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interpretation have introduced bias?

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing 2659 patients were seen and 2585 attended for investigation

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Low risk

NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

References

Included studies

Excluded studies (with excl reason)
Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

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Narrative review

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Not in PICO (non-symptomatic, randomly selected women for prevalence study)


Not in PICO


Not in PICO


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Narrative review


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Narrative review


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Narrative review

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Guideline
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Narrative review

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Not in PICO (but use for pancreatic)


Narrative review


Not in PICO


Not in PICO


Not in PICO/narrative review


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Narrative review


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Not in PICO


Not in PICO


Guideline


Narrative review


Narrative review


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

**Review question:**

Which investigations of symptoms of suspected gall bladder cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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No evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, liver function tests or tumour marker CA19-9 in patients with suspected gall bladder cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)

Narrative review

Not in PICO

Not in PICO
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Narrative review

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Narrative review


Narrative review


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Narrative review


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Not in PICO
Narrative review

In Japanese. Not enough information can be extracted, but it appears to be "Not in PICO".

Not in PICO

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Narrative review

Not in PICO

Russian, no English abstract. Probably not in PICO based on title.

Not in PICO

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Narrative review

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Narrative review

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Not in PICO

Suspected Cancer: Appendix F (June 2015)


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


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Narrative review

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Narrative review

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Not in PICO

Narrative review
LIVER CANCER

Review question:
What is the risk of liver cancer in patients presenting in primary care with symptom(s)?

Results

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Total References retrieved (after de-duplication): 4
Study results

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included studies in the figure below. In one of the included studies, the main issue to note is that the population in the study comprises a mix of ‘old’ and ‘new’ investigated or uninvestigated symptoms, and it is unclear how directly applicable this sample is to the current question. In the other included study, it is unclear whether the patient selection was consecutive. This study also used a sub-optimal reference standard and was also subject to varying degrees of missing data; all of which challenges the validity of the reported results.

<table>
<thead>
<tr>
<th></th>
<th>Risk of Bias</th>
<th>Applicability Concerns</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Patient Selection</td>
<td>Index Test</td>
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<tr>
<td>Hallissey (1990)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>?</td>
<td>+</td>
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Study results

Table 1: Liver cancer: Single symptoms
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.04 (0.002-0.25) 1/2585</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal alanine aminotransferase</td>
<td>All patients</td>
<td>0.46 (0.08-1.8) 2/438</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal aspartate aminotransferase</td>
<td>All patients</td>
<td>0.39 (0.02-2.5) 1/255</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal γ-glutamyltransferase</td>
<td>All patients</td>
<td>0.92 (0.43-1.9) 8/867</td>
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<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal bilirubin</td>
<td>All patients</td>
<td>0 (0-3.2) 0/148</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal alkaline phosphatase</td>
<td>All patients</td>
<td>1.59 (0.41-4.9) 3/189</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal albumin</td>
<td>All patients</td>
<td>0 (0-14) 0/30</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal globulin</td>
<td>All patients</td>
<td>0 (0-8.1) 0/55</td>
</tr>
<tr>
<td>Lilford (2013)</td>
<td>LFT: Abnormal total protein</td>
<td>All patients</td>
<td>0 (0-4.7) 0/97</td>
</tr>
</tbody>
</table>

**Evidence statement(s):**

The positive predictive value for liver cancer ranged from 0% (for abnormal bilirubin/albumin/globulin/total [hepatic] protein) to 1.59% (for abnormal alkaline phosphatase; 2 studies, N = 3875) presenting in primary care was 0.04%. The included studies were associated with 1-3 bias/applicability concerns (see also Table 1).

**Evidence tables**

**Hallissey (1990)**

**PATIENT SELECTION**

**A. risk of bias**

- **Patient sampling**: Prospective consecutive patient series from a group of 10 general practices in England.
- **Was a consecutive or random sample of patients enrolled?**: Yes
- **Was a case-control design avoided?**: Yes
- **Did the study avoid inappropriate exclusions?**: Yes
- **Could the selection of patients have introduced bias?**: Low risk

**B. Concerns regarding applicability**

- **Patient characteristics and setting**: N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.
  - **Inclusion criteria**: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia
  - **Exclusion criteria**: None listed
  - **Clinical setting**: Primary care, England.
<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
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</thead>
</table>

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia of any degree</th>
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<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 4 weeks and follow up.</th>
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<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
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</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>2659 patients were seen and 2585 attended for investigation</th>
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<td>Was there an appropriate interval between index test and reference standard?</td>
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<td>Did all patients receive the same reference standard?</td>
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<td>Were all patients included in the analysis?</td>
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<td>Could the patient flow have introduced bias?</td>
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</table>

### NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).

Lilford (2013)

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective UK study of patients with an abnormal LFT panel across eight primary care practices in Birmingham and three in the Lambeth area of London, UK.</th>
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<tr>
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<td>Was a case-control design avoided?</td>
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<td>Unclear</td>
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<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

| N = 1290; 724 males / 566 females; aged ≤ 34 years: N = 106; 35-44 years: N = 165; 45-54 years: N = 240; 55-64 years: N = 325; 65-74 years: N = 273; 75+ years: N = 181. Reason for testing: Signs and symptoms: N = 406; chronic disease review: N = 884; alcohol at follow up (unit/week): 0: N = 547; 1-14: N = 352; 15-29: N = 153; 30-49: N = 122; 50-99: N = 84; 100+: N = 24; not known: N = 8. Inclusion criteria: Primary care patients without obvious or pre-existing liver disease, and one or more of the eight analytes in an index LFT panel was abnormal. Recruitment took place from 2005 to 2008. Eligible patients were invited to join the study and attend a first follow-up session. Exclusion criteria: None listed. Clinical setting: Primary care, England. |

**Are there concerns that the included patients and setting do not match the review question?**

| Low concern |

**INDEX TEST**

**A. Risk of bias**

**Index test**

| “The index panel comprised: alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), bilirubin (Bili), alkaline phosphatase (ALP), albumin (Alb), globulin (Glob), and total protein (Tprot). Analyte abnormality was determined using standard laboratory reference ranges, which are routinely adjusted for age and gender where appropriate.” The measurement of these was repeated at a first follow up session (taking place a median of 30 days post-first LFT measures (IQR 21-51 days). |

**Were the index test results interpreted without knowledge of the results of the reference standard?**

| Yes |

**Could the conduct or interpretation of the index test have introduced bias?**

| Low risk |

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

| Low concern |

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**

| Diagnosis of any tumours of the hepatobiliary system based on ultrasound of the upper abdomen + exclusion of other hepatic diseases and hepatologist’s opinion along with follow up. |

**Is the reference standard likely to correctly classify the target condition?**

| Unclear |

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

| No |

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

| Unclear risk |

**B. Concerns regarding applicability**

**Are there concerns that the target condition as defined**

| Low concern |
### FLOW AND TIMING

<table>
<thead>
<tr>
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<tr>
<td>Flow and timing</td>
<td>The authors report the results both for the initial testing (that identified the patients in the first place) and for the follow up session (a median of 30 days later). The results reported here are limited to the former, which across the panel of 8 LFTs varied between 977 and 1278 of the included 1290.</td>
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| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | No |
| **Could the patient flow have introduced bias?** | Unclear risk |

**NOTES**

**References**

**Included studies**


**Excluded studies (with excl reason)**


Not in PICO

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Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

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Narrative review

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Narrative review

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Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO (not symptomatic patients presenting to primary care)


Oncology, 12: 13.  
Not in PICO  
Narrative review  
Narrative review  
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Klein, H. M. & Gunther, R. W. (1111) Carcinoma of the gallblader and biliary ducts - What is the value of CT, MRI, and magnetic resonance cholangiography?. [German]. *Chirurgische Gastroenterologie Interdisziplinar*, 20: December.  
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Cancer Practice, 7: 302-308.
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Comment

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Narrative review

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Narrative review
Review question:

Which investigations of symptoms of suspected liver cancer should be done with clinical responsibility retained by primary care?

Results

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References

Included studies

Excluded studies (with excl reason)


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Narrative review

Narrative review

Not in PICO

In Japanese. Not enough information can be extracted, but don't think it is in PICO

Narrative review

In Japanese, not enough information can be extracted to ascertain relevance, but I think it is not in PICO

Not in PICO

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Narrative review

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Narrative review

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Narrative review

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Guideline


Guideline/duplicate


Guideline


Narrative review


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Narrative review


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Narrative review

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In Japanese. Not enough information can be extracted to ascertain eligibility status


Not in PICO


Narrative review


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Narrative review

of radiologic findings and histopathology for the diagnosis of hepatocellular carcinoma. *Hepatology*, 56: 484A.

Not in PICO


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Narrative review


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49.
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Comment
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Same data as other included Lilford paper
Asked Willie 9/1290 had cancer, but these may be known cancers (4 metastatic ), i.e, patients selected who LFTs done to
Narrative review
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Unavailable, but I think it is not in PICO
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Narrative review


Narrative review


Narrative review


Narrative review


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Narrative review


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Not in PICO (The study refers to 45 patients with liver tumors, including 12 with malignant tumors primitive, 15 with liver metastases and 18 with benign liver tumors.)


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Narrative review


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Narrative review


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Narrative review
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## LOWER GASTRO-INTESTINAL TRACT CANCERS

### COLORECTAL CANCER

**Review question:**
What is the risk of colorectal cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
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**Update Search**

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Total References retrieved (after de-duplication): 70
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note relates to patient selection and applicability with some studies employing non-consecutive patient sampling, e.g., case-control designs (which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection), and others being conducted in setting or with patients that may not directly translate to the current question and UK-based primary care. The other main issues of concern relates to missing data (and the concern that this may not be missing at random) and under specification of symptoms and reference standards, which makes it difficult to ascertain their applicability and/or validity.
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### Study results

#### Table 1: Colorectal cancer: Meta-analyses

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<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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</table>
Please note that the data from Hamilton (2005, 2008, 2009) are not included in these meta-analyses due to the case-control design of the studies. These data are instead reported in the table below. In addition, sensitivity analyses were conducted where the studies with a high risk of patient selection bias were excluded. When the number of studies was < 3, the data were not meta-analysed, but presented for the individual studies instead.

Table 2: Colorectal cancer: Individual positive predictive values from the meta-analyses

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Table 3: Colorectal cancer: Additional results reported by the individual papers: Individual symptoms
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<td>All patients</td>
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<td>Diarrhoea (reported twice)</td>
<td>All patients</td>
<td>1.5 (1-2.2)</td>
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<tr>
<td>Panzuto (2003)</td>
<td>Bloating</td>
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<td>Change in bowel habit</td>
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<td>Loss of appetite</td>
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<tr>
<td>Hamilton (2005)</td>
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<td>All patients</td>
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<tr>
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<td>Non-acute abdominal complaints</td>
<td>All patients</td>
<td>0.52 (0.1-1.6) 3/578</td>
</tr>
<tr>
<td>Muris (1995)</td>
<td>Non-acute abdominal complaints</td>
<td>All patients</td>
<td>0.43 (0.1-1.2) 4/933</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abnormal rectal exam (reported once)</td>
<td>All patients</td>
<td>1.5 (1-2.2) Cases: 51/349 Controls: 67/1744</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoglobin 10-13 g dl⁻¹ (reported once)</td>
<td>All patients</td>
<td>0.97 (0.8-1.3) Cases: 55/349 Controls: 69/1744</td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 10-12.9 g dl⁻¹</td>
<td>All patients</td>
<td>0.3 (0.2-0.3) Cases: 503/3421 Controls: 996/23928</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoglobin &lt; 10 g dl⁻¹ (reported once)</td>
<td>All patients</td>
<td>2.3 (1.6-3.1) Cases: 40/349 Controls: 21/1744</td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin &lt; 9.9 g dl⁻¹</td>
<td>All patients</td>
<td>2 (1.7-2.3) Cases: 296/3421 Controls: 96/23928</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Haemoglobin 12-12.9 g dl⁻¹</td>
<td>All patients</td>
<td>Cases: 17/349 Controls: 20/1744</td>
</tr>
</tbody>
</table>
Hamilton (2005)  | Haemoglobin 10-11.9 g dl⁻¹  | All patients  | Cases: 38/349  
|                |                          | Controls: 49/1744  
Hamilton (2005)  | Haemoglobin < 10 g dl⁻¹  | All patients  | Cases: 40/349  
|                |                          | Controls: 21/1744  
Hamilton (2005)  | Positive faecal occult blood  | All patients  | Cases: 31/79  
|                |                          | Controls: 5/47  
Hamilton (2005)  | Blood sugar > 10 mmol l⁻¹  | All patients  | Cases: 25/349  
|                |                          | Controls: 39/1744  
Oudega (2006)  | Deep vein thrombosis  | All patients  | 0.7 (0.2-2.2)  
|                |                          | 3/430  
Hamilton (2005)  | History of diabetes  | All patients  | Cases: 37/349  
|                |                          | Controls: 119/1744  

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 4: Colorectal cancer: Additional results reported by the individual papers: Rectal bleeding with other symptoms/signs

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and constipation</td>
<td>All patients</td>
<td>2.4 (1.4-4.4)</td>
</tr>
<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding and constipation</td>
<td>All patients</td>
<td>2.6 (0.1-15.1)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and diarrhoea</td>
<td>All patients</td>
<td>3.4 (2.1-6)</td>
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<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding and diarrhoea</td>
<td>All patients</td>
<td>7.4 (1.3-25.8)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and abdominal tenderness</td>
<td>All patients</td>
<td>4.5 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and abnormal rectal exam</td>
<td>All patients</td>
<td>8.5 (NR)</td>
</tr>
<tr>
<td>Wauters (2000)</td>
<td>Rectal bleeding and fatigue</td>
<td>All patients</td>
<td>7.1 (??)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and haemoglobin 10-13 g dl⁻¹</td>
<td>All patients</td>
<td>3.6 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and haemoglobin &lt; 10 g dl⁻¹</td>
<td>All patients</td>
<td>3.2 (NR)</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding and change in bowel habit</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>9.2 (4.9-16.3) 11/119</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and change in bowel habit</td>
<td>All patients</td>
<td>11 (NR)</td>
</tr>
<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding and change in bowel habit</td>
<td>All patients</td>
<td>10.3 (3.3-25.2) 4/39</td>
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<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed bowel habit</td>
<td>All patients</td>
<td>26.85 (19-36.4)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptoms and Change in Habit</td>
<td>Study Details</td>
<td>All Patients</td>
</tr>
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<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and uncertain change in bowel habit</td>
<td>All patients</td>
<td>25 (8.3-52.6)</td>
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<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and no change in bowel habit</td>
<td>All patients</td>
<td>25 (8.3-52.6)</td>
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<td>Rectal bleeding and no change in bowel habit</td>
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<td>Mant (1989)</td>
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<td>11 (NR)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and increased frequency/loose motions</td>
<td>All patients</td>
<td>4.8 (2.7-8.3)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and no ‘increased frequency/loose motions’</td>
<td>All patients</td>
<td>2.8 (1.4-5.5)</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding and change in bowel habit (hard ± infrequent)</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>2.8 (0.1-16.2)</td>
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<td>Ellis (2005)</td>
<td>Rectal bleeding and no perianal symptoms</td>
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<td>11.1 (5-22.2)</td>
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<td>Ellis (2005)</td>
<td>Rectal bleeding and perianal symptoms</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding and feeling of incomplete evacuation of rectum</td>
<td>All patients</td>
<td>12 (NR)</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and no feeling of incomplete evacuation of rectum</td>
<td>All patients</td>
<td>11 (NR)</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding and pain on defecation</td>
<td>All patients</td>
<td>7 (NR)</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding and no pain on defecation</td>
<td>All patients</td>
<td>12 (NR)</td>
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<tr>
<td>Wauters (2000)</td>
<td>Rectal bleeding and spasm</td>
<td>All patients</td>
<td>5.4 (2-11.4)</td>
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<td>Patient Population</td>
<td>Ratio or Count</td>
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<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and uncertain discomfort</td>
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<td>23.08 (9.8-44.1) 6/26</td>
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<td>13.22 (9.3-18.3) 32/242</td>
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<td>Ellis (2005)</td>
<td>Rectal bleeding and change in bowel habit and abdominal pain</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>9 (3.7-19.1) 6/67</td>
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<td>9.6 (3.6-21.8) 5/52</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Dark blood</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>9.7 (2.5-26.9) 3/31</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding: Dark blood</td>
<td>All patients</td>
<td>19 (NR)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Dark blood</td>
<td>All patients</td>
<td>7.4 (3.7-14) 9/121</td>
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<td>Metcalf (1996)</td>
<td>Rectal bleeding: Dark red blood loss</td>
<td>All patients</td>
<td>9.7 (2.5-26.9) 3/31</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: No/not dark blood</td>
<td>All patients</td>
<td>2.7 (1.5-4.7) 13/483</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Bright blood</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>4 (1.9-8.1) 8/199</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding: Bright blood</td>
<td>All patients</td>
<td>10 (NR)</td>
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<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding: Bright red blood loss</td>
<td>All patients</td>
<td>8.6 (3.5-18.4) 6/70</td>
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<td>Ellis (2005)</td>
<td>Rectal bleeding: Blood on paper only</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>2.4 (0.4-9.4) 2/82</td>
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<td>Rectal bleeding: Blood seen on paper</td>
<td>All patients</td>
<td>9 (NR)</td>
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<td>Metcalf (1996)</td>
<td>Rectal bleeding: Blood only on paper</td>
<td>All patients</td>
<td>8.3 (1.5-28.5) 2/24</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding: Blood seen in toilet bowl</td>
<td>All patients</td>
<td>14 (NR)</td>
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<td>Ellis (2005)</td>
<td>Rectal bleeding: Blood seen in toilet bowl and on paper</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>4.9 (2.4-9.4) 9/184</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding: Blood seen on paper and in toilet bowl</td>
<td>All patients</td>
<td>11 (NR)</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Large volume of blood</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>1.3 (0.07-7.8) 1/79</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Small volume of blood</td>
<td>Patients with flexible sigmoidoscopy/</td>
<td>5.3 (2.7-9.9) 10/187</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Description</td>
<td>Group</td>
<td>Data Source</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: First time</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>4.7 (1.7-11.2)</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Not first time</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>3.8 (1.5-8.3)</td>
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<tr>
<td>Nørrelund (1996)</td>
<td>Rectal bleeding: Not first time, unchanged bleeding pattern</td>
<td>All patients</td>
<td>4.4 (0.8-16.4)</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>Rectal bleeding: Not first time, changed bleeding pattern</td>
<td>All patients</td>
<td>18.75 (9.4-33.1)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding: Blood on stool or mixed with stool</td>
<td>All patients</td>
<td>7 (NR)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding: Blood mixed with stool only</td>
<td>All patients</td>
<td>14 (NR)</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding: Blood seen mixed with faeces</td>
<td>All patients</td>
<td>21 (NR)</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Blood mixed with the stool</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>3 (0.2-17.5)</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Blood mixed with stool</td>
<td>All patients</td>
<td>5.4 (3.3-8.7)</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding: Others or combinations apart from “blood on stool or mixed with stool only”</td>
<td>All patients</td>
<td>1 (NR)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Not ‘dark blood and blood mixed with stool’</td>
<td>All patients</td>
<td>2.5 (1.4-4.4)</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Blood neither dark nor mixed with stool</td>
<td>All patients</td>
<td>1.9 (0.7-4.7)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Not ‘blood neither dark nor mixed with stool’</td>
<td>All patients</td>
<td>4.9 (3-7.9)</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding: Unknown how blood was seen</td>
<td>All patients</td>
<td>7 (NR)</td>
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<tr>
<td>Study</td>
<td>Symptom Description</td>
<td>Population</td>
<td>Odds Ratio</td>
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<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding: Blood not mixed with the stool</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>4.3 (2.2-8)</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding: Blood not mixed with stool</td>
<td>All patients</td>
<td>1.7 (0.6-4.2)</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding: Blood seen separate from faeces</td>
<td>All patients</td>
<td>7 (NR)</td>
</tr>
<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding and associated slime</td>
<td>All patients</td>
<td>10.7 (2.8-29.4)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and nausea</td>
<td>All patients</td>
<td>2 (NR)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and abdominal pain</td>
<td>All patients</td>
<td>2 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding and abdominal pain</td>
<td>All patients</td>
<td>3.1 (1.9-5.3)</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and abdominal pain</td>
<td>All patients</td>
<td>9 (NR)</td>
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<td>Rectal bleeding and abdominal pain</td>
<td>All patients</td>
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<td>All patients</td>
<td>1.7 (0.6-4.6)</td>
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<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and abdominal pain</td>
<td>All patients</td>
<td>23.33 (15.3-33.7)</td>
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<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Rectal bleeding and dyspepsia</td>
<td>All patients</td>
<td>2.6 (1.1-5.9)</td>
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<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Rectal bleeding (visible blood in stools only) and dyspepsia</td>
<td>All patients</td>
<td>4 (1.5-9.6)</td>
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<tr>
<td>Nørrelund (1996)</td>
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<td>All patients</td>
<td>22.22 (3.9-59.8)</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding and no abdominal pain</td>
<td>All patients</td>
<td>12 (NR)</td>
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<td>Robertson (2006)</td>
<td>Rectal bleeding and no abdominal pain</td>
<td>All patients</td>
<td>4.5 (2.7-7.3)</td>
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<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and no abdominal pain</td>
<td>All patients</td>
<td>11.7 (8.2-16.3)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and decreased appetite</td>
<td>All patients</td>
<td>2 (NR)</td>
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<td>Fijten (1995)</td>
<td>Rectal bleeding and pain at night</td>
<td>All patients</td>
<td>0 (0-8.9)</td>
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<td>Wauters (2000)</td>
<td>Rectal bleeding and pain</td>
<td>All patients</td>
<td>0 (0-10.2)</td>
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<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and weight loss</td>
<td>All patients</td>
<td>10 (NR)</td>
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<td>Hamilton (2005)</td>
<td>Rectal bleeding and weight loss</td>
<td>All patients</td>
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<td>Population</td>
<td>Odds Ratio (Range)</td>
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<td>Robertson (2006)</td>
<td>Rectal bleeding and weight loss</td>
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<td>Rectal bleeding and weight loss</td>
<td>All patients</td>
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<td>Metcalf (1996)</td>
<td>Rectal bleeding and weight loss</td>
<td>All patients</td>
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<td>16 (4.5-36.1)</td>
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<td>All patients</td>
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<td>Rectal bleeding and nongastrointestinal symptoms</td>
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<td>Rectal bleeding and perianal eczema</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding and no anal itch</td>
<td>All patients</td>
<td>14 (NR)</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and haemorrhoid on rectal palpation</td>
<td>All patients</td>
<td>10 (NR)</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and haemorrhoids identified by GP</td>
<td>All patients</td>
<td>5 (NR)</td>
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<td>Robertson (2006)</td>
<td>Rectal bleeding and haemorrhoids</td>
<td>All patients</td>
<td>3.1 (1.6-5.9) 10/320</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and haemorrhoids and bright red blood not mixed with stools</td>
<td>All patients</td>
<td>1.9 (0.5-5.8) 3/159</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and all patients</td>
<td>All patients</td>
<td>3.3 (0.9-10.1)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptoms and Findings</td>
<td>Case Count</td>
<td>Positive Cases</td>
</tr>
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<td>--------------------------------------------------------------------------------------</td>
<td>------------</td>
<td>----------------</td>
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<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and no haemorrhoids identified by GP</td>
<td>All patients</td>
<td>17 (NR)</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and no haemorrhoids</td>
<td>All patients</td>
<td>4.6 (2.4-8.3) 11/239</td>
</tr>
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<td>Robertson (2006)</td>
<td>Rectal bleeding and no haemorrhoids and no other symptoms except bright non-mixed bleeding’</td>
<td>All patients</td>
<td>4.5 (2.8-7.2) 18/400</td>
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<td>Robertson (2006)</td>
<td>Rectal bleeding and no ‘haemorrhoids and bright red blood not mixed with stools’</td>
<td>All patients</td>
<td>3.8 (2.4-6.1) 18/469</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and tumour on rectal palpation</td>
<td>All patients</td>
<td>100 (NR) Total positives N = 1 (but out of 208, not 269)</td>
</tr>
<tr>
<td>Wauters (2000)</td>
<td>Rectal bleeding and palpable tumour</td>
<td>All patients</td>
<td>31.5 (12.5-56.5)</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and anal protrusion noticed by patient</td>
<td>All patients</td>
<td>3 (NR)</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and no anal protrusion noticed by patient</td>
<td>All patients</td>
<td>13 (NR)</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and abnormal prostate on rectal palpation</td>
<td>All patients</td>
<td>50 (NR) Total positive N = 2 (but out of 208, not 269)</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and previous history of rectal bleeding</td>
<td>All patients</td>
<td>0 (0-4.8) Total positives N = 96</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and first degree relative with colorectal cancer</td>
<td>All patients</td>
<td>10 (NR)</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding and no first degree relative with colorectal cancer</td>
<td>All patients</td>
<td>11 (NR)</td>
</tr>
<tr>
<td>Metcalf (1996)</td>
<td>Rectal bleeding and family history of bowel cancer</td>
<td>All patients</td>
<td>0 (0-40.2) 0/8</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and family history of abdominal disease</td>
<td>All patients</td>
<td>0 (0-5.5) Total positives N = 83</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and history of irritable bowel</td>
<td>All patients</td>
<td>0 (0-4.8) 0/96</td>
</tr>
<tr>
<td>Study</td>
<td>Symptom(s)</td>
<td>Patient group</td>
<td>Positive predictive value, % (95% CI)</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------</td>
<td>---------------</td>
<td>---------------------------------------</td>
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<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and no history of irritable bowel syndrome</td>
<td>All patients</td>
<td>4.4 (2.8-6.7) 21/481</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and history of diverticular disease</td>
<td>All patients</td>
<td>0 (0-12.6) 0/34</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and no history of diverticular disease</td>
<td>All patients</td>
<td>3.9 (2.5-6) 21/536</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding and abnormal proctoscopy</td>
<td>All patients</td>
<td>0 (0-14.1) Total positives N = 30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(but out of 45, not 269)</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding and deprivation category (deprivation category 1 = least deprived, deprivation category 7 = most deprived)</td>
<td>Deprivation category 1</td>
<td>4.1 (1.1-12.2) 3/74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deprivation category 2</td>
<td>3.4 (1.1-8.9) 4/119</td>
</tr>
<tr>
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<td></td>
<td>Deprivation category 3</td>
<td>2.6 (0.8-6.9) 4/155</td>
</tr>
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<td></td>
<td>Deprivation category 4</td>
<td>5.8 (2.7-11.6) 8/137</td>
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<td>Deprivation category 5</td>
<td>0/53 (0-8.4)</td>
</tr>
<tr>
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<td></td>
<td>Deprivation category 6</td>
<td>0/25 (0-16.6)</td>
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<tr>
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<td></td>
<td>Deprivation category 7</td>
<td>5.3 (0.3-28.1) 1/19</td>
</tr>
</tbody>
</table>

Please note:
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported.

Table 5: Colorectal cancer: Additional results reported by the individual papers: Other symptom combinations
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom Combination</th>
<th>Population</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and loss of weight</td>
<td>All patients</td>
<td>3.1 (1.8-5.5)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and abdominal pain</td>
<td>All patients</td>
<td>1.9 (1.4-2.7)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and abdominal tenderness</td>
<td>All patients</td>
<td>2.4 (1.3-4.8)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and abnormal rectal exam</td>
<td>All patients</td>
<td>11 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and haemoglobin 10-13 g dl⁻¹</td>
<td>All patients</td>
<td>2.2 (1.2-4.3)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea and haemoglobin &lt; 10 g dl⁻¹</td>
<td>All patients</td>
<td>2.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain and loss of weight</td>
<td>All patients</td>
<td>3.4 (2.1-6)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain and abdominal tenderness</td>
<td>All patients</td>
<td>1.4 (0.3-2.2)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain and abnormal rectal exam</td>
<td>All patients</td>
<td>3.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain and haemoglobin 10-13 g dl⁻¹</td>
<td>All patients</td>
<td>2.2 (1.1-4.5)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain and haemoglobin &lt; 10 g dl⁻¹</td>
<td>All patients</td>
<td>6.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal tenderness and loss of weight</td>
<td>All patients</td>
<td>6.4 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal tenderness and abnormal rectal exam</td>
<td>All patients</td>
<td>5.8 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal tenderness and haemoglobin 10-13 g dl⁻¹</td>
<td>All patients</td>
<td>2.7 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal tenderness and haemoglobin &lt; 10 g dl⁻¹</td>
<td>All patients</td>
<td>&gt;10 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Loss of weight and abnormal rectal exam</td>
<td>All patients</td>
<td>7.4 (NR)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Loss of weight and haemoglobin 10-13 g dl⁻¹</td>
<td>All patients</td>
<td>1.3 (0.7-2.6)</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Loss of weight and haemoglobin &lt; 10 g dl⁻¹</td>
<td>All patients</td>
<td>4.7 (NR)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and anaemia</td>
<td>All patients</td>
<td>13.51 (5-29.57)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and dysphagia</td>
<td>All patients</td>
<td>0 (0-2.2)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and jaundice</td>
<td>All patients</td>
<td>0 (0-48.32)</td>
</tr>
<tr>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia and weight loss</td>
<td>All patients</td>
<td>1.37 (0.35-4.28)</td>
</tr>
</tbody>
</table>

Please note:
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = not reported.
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du Toit (2006)</td>
<td>Rectal bleeding</td>
<td>Patients 45-54 years</td>
<td>3.9 (0.7-14.6) 2/51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 55-64 years</td>
<td>1.3 (0.07-8.2) 1/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 65-74 years</td>
<td>9.5 (3.9-20.2) 6/63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients ≥ 75 years</td>
<td>7.9 (3.3-17) 6/76</td>
</tr>
<tr>
<td>Ellis (2005)</td>
<td>Rectal bleeding and aged ≥ 60 years</td>
<td>Patients with flexible sigmoidoscopy/questionnaire data</td>
<td>5.2 (2.4-10.3) 8/155</td>
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<tr>
<td></td>
<td>Rectal bleeding and aged ≤ 59 years</td>
<td></td>
<td>1.8 (0.5-5.7) 3/164</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding</td>
<td>Patients 18-59 years</td>
<td>0.4 (0.03-2.8) 1/229</td>
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<tr>
<td></td>
<td></td>
<td>Patients 60-75 years</td>
<td>20 (9.6-36.1) 8/40</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding</td>
<td>Patients 40-69 years</td>
<td>7.87 (5-12.1) 20/254</td>
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<tr>
<td></td>
<td></td>
<td>Patients 70-79 years</td>
<td>34.12 (24.4-45.3) 29/85</td>
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<tr>
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<td></td>
<td>Patients 80+ years</td>
<td>20 (7.6-41.3) 5/25</td>
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<tr>
<td>Hamilton (2005)</td>
<td>Rectal bleeding</td>
<td>Patients 40-69 years</td>
<td>1.4 (NR) 4/228</td>
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<tr>
<td></td>
<td></td>
<td>Patients ≥ 70 years</td>
<td>4.8 (NR) 15/328</td>
</tr>
<tr>
<td>Heintze (2005)</td>
<td>Rectal bleeding</td>
<td>Patients &lt; 50 years</td>
<td>2/≤153*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients ≥ 50 years</td>
<td>15/≤268*</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding</td>
<td>Patients 40-60 years</td>
<td>8 (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients &gt; 60 years</td>
<td>16 (NR)</td>
</tr>
<tr>
<td>Parker (2007)</td>
<td>Rectal bleeding</td>
<td>Patients 25-34 years</td>
<td>0.1 3/4717</td>
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<td></td>
<td>Patients 35-44 years</td>
<td>0.3 17/5301</td>
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<td>Patients 45-54 years</td>
<td>1.5 (1.2-1.8) 75/5120</td>
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<td>Patients 55-64 years</td>
<td>2.8 (2.3-3.3) 137/4927</td>
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<td>Patients 65-74 years</td>
<td>4.3 (3.7-5) 189/4383</td>
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<td></td>
<td>Patients 75-84 years</td>
<td>5.5 (4.7-6.3) 173/3168</td>
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<td></td>
<td></td>
<td>Patients ≥ 85 years</td>
<td>3.7 (2.8-4.8) 51/1391</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding</td>
<td>Patients &lt; 50 years</td>
<td>1.1 (0.3-3.5) 3/270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 50-69 years</td>
<td>4.8 (2.6-8.7)</td>
</tr>
<tr>
<td>Study</td>
<td>Symptom</td>
<td>Age Group</td>
<td>RR</td>
</tr>
<tr>
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<td>----------------------------------------------</td>
<td>--------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Wauters (2000)</td>
<td>Rectal bleeding</td>
<td>Patients &lt; 50 years</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 50-59 years</td>
<td>1.7</td>
</tr>
<tr>
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<td></td>
<td>Patients 60-69 years</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 70-79 years</td>
<td>21.2</td>
</tr>
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<td></td>
<td>Patients ≥ 80 years</td>
<td>5.8</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and change in bowel habit</td>
<td>Patients 40-69 years</td>
<td>16.13</td>
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<td></td>
<td></td>
<td>Patients 70-79 years</td>
<td>42.5</td>
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<td>Patients 80+ years</td>
<td>33.3</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and uncertain change in bowel habit</td>
<td>Patients 40-69 years</td>
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<td>Patients 70-79 years</td>
<td>66.7</td>
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<td>Patients 80+ years</td>
<td>0</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding and no change in bowel habit</td>
<td>Patients 40-69 years</td>
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<td>Patients 70-79 years</td>
<td>23.81</td>
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<td>Patients 80+ years</td>
<td>17.65</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Abdominal pain</td>
<td>Patients 40-69 years</td>
<td>0.65</td>
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<td></td>
<td>Patients ≥ 70 years</td>
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<tr>
<td>Hamilton (2005)</td>
<td>Diarrhoea</td>
<td>Patients 40-69 years</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients ≥ 70 years</td>
<td>1.7</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Constipation</td>
<td>Patients 40-69 years</td>
<td>0.2</td>
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<tr>
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<td></td>
<td>Patients ≥ 70 years</td>
<td>1.3</td>
</tr>
<tr>
<td>Hamilton (2005)</td>
<td>Weight loss</td>
<td>Patients 40-69 years</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients ≥ 70 years</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Data missing from 22/422 patients, but it is unclear which of the age subgroups the missing data belongs to.*

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies.

Table 7: Colorectal cancer: Additional results reported by the individual papers: Men
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins (2012)</td>
<td>Rectal bleeding</td>
<td>Men 30-84 years</td>
<td>2.8 (2.6-3) 791/28423</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Rectal bleeding at 6 months</td>
<td>Men (all ages)</td>
<td>1.8 (15-2.2) 138/7523</td>
</tr>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding</td>
<td>Men (all ages)</td>
<td>5.9 (2.6-12.3) 7/118</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Rectal bleeding at 3 years</td>
<td>Men (all ages)</td>
<td>2.4 (2.1-2.8) 184/7523</td>
</tr>
<tr>
<td>Mant (1989)</td>
<td>Rectal bleeding</td>
<td>Men ≥ 40 years</td>
<td>9 (NR)</td>
</tr>
<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding</td>
<td>Men ≥ 40 years</td>
<td>17.26 (12-24) 29/168</td>
</tr>
<tr>
<td>Robertson (2006)</td>
<td>Rectal bleeding</td>
<td>Men (all ages)</td>
<td>4.8 (2.7-8.2) 13/273</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Rectal bleeding at 3 years</td>
<td>Men &lt; 45 years</td>
<td>0.07 (0.01-0.27) 2/2701</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men 45-54 years</td>
<td>1.56 (1-2.31) 24/1542</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men 55-64 years</td>
<td>3.38 (2.47-4.51) 44/1302</td>
</tr>
<tr>
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<td>Men 65-74 years</td>
<td>4.8 (3.65-6.17) 57/1188</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men 75-84 years</td>
<td>7.74 (5.78-10.1) 49/633</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men ≥ 85 years</td>
<td>5.1 (2.23-9.79) 8/157</td>
</tr>
<tr>
<td>Hamilton (2009)</td>
<td>Rectal bleeding at 2 years (read off graph)</td>
<td>Men &lt; 60 years</td>
<td>0.5 (0.3-0.7) 2/400</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men 60-69 years</td>
<td>2.4 (1.8-3.2) 24/1542</td>
</tr>
<tr>
<td></td>
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<td>Men 70-79 years</td>
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<td>Age Group</td>
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<td>Haemoglobin ≥ 13 g dl⁻¹</td>
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<td>Men 60-69 years</td>
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<td>Men ≥ 80 years</td>
<td>0.4 (0.3-0.5)</td>
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<td>0.7 (0.5-1)</td>
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<td>Men 70-79 years</td>
<td>1 (0.7-1.2)</td>
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<td>Men ≥ 80 years</td>
<td>0.6 (0.5-0.8)</td>
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<td>Hamilton (2008)</td>
<td>Haemoglobin 11-11.9 g dl⁻¹</td>
<td>Men 30-59 years</td>
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<td>Men 60-69 years</td>
<td>1.4 (0.9-2.3)</td>
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<td>Men 70-79 years</td>
<td>1.5 (1.2-2)</td>
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<td>Men ≥ 80 years</td>
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<td>Hamilton (2008)</td>
<td>Haemoglobin 10-10.9 g dl⁻¹</td>
<td>Men 30-59 years</td>
<td>0.8 (0.3-2.2)</td>
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<td>Men 60-69 years</td>
<td>2.3 (1.1-4.8)</td>
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<td>Men 70-79 years</td>
<td>3.2 (2.2-4.8)</td>
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<td>1.6 (1.1-2.2)</td>
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<td>Men ≥ 80 years</td>
<td>6 (3.4-10)</td>
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<td>Haemoglobin &lt; 9 g dl⁻¹</td>
<td>Men 30-59 years</td>
<td>1.3 (0.4-4.3)</td>
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<td>7.6 (3.4-16)</td>
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<td>Men 70-79 years</td>
<td>8.8 (5.4-14)</td>
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### Table 8: Colorectal cancer: Additional results reported by the individual papers: Women

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins (2012)</td>
<td>Rectal bleeding</td>
<td>Women 30-84 years</td>
<td>2.1 (1.9-2.2)</td>
</tr>
<tr>
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<td>571/27811</td>
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<tr>
<td>Yates (2004)</td>
<td>Anaemia</td>
<td>Men &gt; 20 years</td>
<td>18.2 (12.6-25.4)</td>
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<td></td>
<td>28/154</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men 50-59 years</td>
<td>1.86 (NR)</td>
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<td>Men 60-69 years</td>
<td>3.02 (NR)</td>
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<td>Men 70-79 years</td>
<td>3.38 (NR)</td>
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<td>Men 80-89 years</td>
<td>2.98 (NR)</td>
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</tbody>
</table>

**For the 30-59 years group 64 cases, but only 11 controls had markers of iron deficiency making meaningful analysis impossible.**

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using \(\frac{TP}{TP+FP}\) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NP = Not reported.
<table>
<thead>
<tr>
<th>Study</th>
<th>Event Description</th>
<th>Age Group</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fijten (1995)</td>
<td>Rectal bleeding</td>
<td>Women (all ages)</td>
<td>1.3 (0.2-5.2)</td>
<td>2/151</td>
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<td>(0.2-5.2)</td>
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<tr>
<td>Jones (2007)</td>
<td>Rectal bleeding at 3 years</td>
<td>Women (all ages)</td>
<td>2 (1.7-2.3)</td>
<td>154/7766</td>
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<td>(1.7-2.3)</td>
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<td>Mant (1989)</td>
<td>Rectal bleeding</td>
<td>Women ≥ 40 years</td>
<td>13 (NR)</td>
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<tr>
<td>Nørrelund (1996)</td>
<td>New onset or changed pattern rectal bleeding</td>
<td>Women ≥ 40 years</td>
<td>12.76 (8.6-18.4)</td>
<td>25/196</td>
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<td>Robertson (2006)</td>
<td>Rectal bleeding</td>
<td>Women (all ages)</td>
<td>2.7 (1.3-5.3)</td>
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<td>Jones (2007)</td>
<td>Rectal bleeding at 3 years</td>
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<td>(0.27-1.24)</td>
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<td>Women 55-64 years</td>
<td>2.75 (1.9-3.84)</td>
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<td>Women 65-74 years</td>
<td>2.42 (1.62-3.48)</td>
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<td>Women 75-84 years</td>
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<td></td>
<td>Women ≥ 80 years</td>
<td>0.9 (0.8-1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.8-1)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2009)</td>
<td>Diarrhoea (read off graph)</td>
<td>Women &lt; 60 years</td>
<td>0.01 (0.1-0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.1-0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women 60-69 years</td>
<td>0.35 (0.25-0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.25-0.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women 70-79 years</td>
<td>0.5 (0.4-0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.4-0.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women ≥ 80 years</td>
<td>0.7 (0.6-0.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.6-0.8)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2009)</td>
<td>Constipation (read off)</td>
<td>Women &lt; 60 years</td>
<td>0.1 (0.1-0.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(0.1-0.1)</td>
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</tr>
<tr>
<td>Source</td>
<td>Condition</td>
<td>Age Group</td>
<td>Value Range</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Collins (2012)</td>
<td>Appetite loss</td>
<td>Women 30-84 years</td>
<td>0.6 (0.4-1)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2009)</td>
<td>Weight loss 5-10%</td>
<td>Women &lt; 60 years</td>
<td>0.05 (0.05-0.05)</td>
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<tr>
<td>Hamilton (2009)</td>
<td>Weight loss ≥ 10%</td>
<td>Women &lt; 60 years</td>
<td>0.06 (0.06-0.08)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin ≥ 13 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0 (0-0)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 12-12.9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0.0 (0.0-0.1)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 11-11.9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0.1 (0.1-0.2)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 10-10.9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0.1 (0.1-0.2)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 9-9.9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0.9 (0.3-2.9)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin &lt; 9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>&gt;5 (41 cases, 0 controls)</td>
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</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin ≥ 13 g dl⁻¹ + indicators of iron deficiency</td>
<td>Women 30-59 years</td>
<td>0.1 (0-0.3)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 12-12.9 g dl⁻¹ + indicators of iron deficiency</td>
<td>Women 30-59 years</td>
<td>0.1 (0-0.3)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008)</td>
<td>Haemoglobin 11-11.9 g dl⁻¹</td>
<td>Women 30-59 years</td>
<td>0.2 (0.1-0.4)</td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008) Haemoglobin 10-10.9 g dl⁻¹ + indicators of iron deficiency</td>
<td>Women 60-69 years</td>
<td>1.5 (0.7-3.3)</td>
<td></td>
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<td>---</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 70-79 years</td>
<td>2.1 (1.1-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women ≥ 80 years</td>
<td>3.6 (2.6-5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008) Haemoglobin 9-9.9 g dl⁻¹ + indicators of iron deficiency</td>
<td>Women 30-59 years</td>
<td>0.3 (0.1-0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 60-69 years</td>
<td>3.5 (1.1-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 70-79 years</td>
<td>8.6 (3.8-18)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Women ≥ 80 years</td>
<td>5.7 (3-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008) Haemoglobin &lt; 9 g dl⁻¹ + indicators of iron deficiency</td>
<td>Women 30-59 years</td>
<td>0.6 (0.2-2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 60-69 years</td>
<td>&gt;5 (36 cases, 0 controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 70-79 years</td>
<td>10 (5.2-19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women ≥ 80 years</td>
<td>10 (5.6-17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamilton (2008) Haemoglobin &lt; 10 g dl⁻¹</td>
<td>Women &gt; 60 years</td>
<td>7.7 (5.7-11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cases: 367/3021</td>
<td>121/21138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collins (2012) Anaemia</td>
<td>Women 30-84 years</td>
<td>1.3 (1.1-1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>173/13659</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yates (2004) Anaemia</td>
<td>Women &gt; 50 years</td>
<td>3.2 (1.6-6.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9/277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawrenson (2006) Anaemia</td>
<td>Women 40-49 years</td>
<td>0.08 (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 50-59 years</td>
<td>0.56 (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 60-69 years</td>
<td>1.38 (NR)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Women 70-79 years</td>
<td>1.99 (NR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women 80-89 years</td>
<td>2.01 (NR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please note:
- Lawrenson (2006) calculated the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting by using Kaplan-Maier curves, and it is unclear how and if these calculations differ from those of the other studies.
- The calculations of the positive predictive values differ between the remaining studies using (TP)/(TP+FP) and Hamilton (2005, 2008, 2009) using other statistics due to the case-control design of these studies. NR = Not reported

**Evidence statement(s):**

Rectal bleeding (16 studies, N = 134794) presenting in a primary care setting is associated with an overall positive predictive value of up to 4.88% for colorectal cancer, which tended to increase with age (10 studies, N = 33874) both in men (3 studies, N = 103846) and in women (3 studies, N = 103846). All the studies were associated with ≤ 2 bias or applicability concerns (see also Tables 1-3, 6-8).

Abdominal pain (5 studies, N = 373796) presenting in a primary care setting is associated with an overall positive predictive value of up to 2.04% for colorectal cancer, which tended to increase with age (1 study, N = 2093) both in men (1 study, N = 43791) and in women (1 study, N = 43791). All the studies were associated with ≤ 2 bias or applicability concerns (see also Tables 1-3, 6-8).
Anaemia (10 studies, N = 89550) presenting in a primary care setting is associated with an overall positive predictive value of up to 5.87% for colorectal cancer, which tended to increase with age (1 study, N = 2093) both in men (2 studies, N = 118672) and in women (2 studies, N = 118672). Seven of the studies were associated with ≤ 2 bias or applicability concern, while the remaining two studies were associated with 3 and 4 bias or applicability concerns, respectively (see also Tables 1-3, 7-8).

Constipation (2 studies, N = 2373) presenting in a primary care setting is associated with an overall positive predictive value of up to 15.7% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 0.42-0.81% reported by another study (N = 2093) that also showed that the positive predictive values increase with age, which seems to be the case for both men (1 study, N = 43791) and for women (1 study, N = 43791). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 1-3, 6-8).

Diarrhoea (2 studies, N = 2373) presenting in a primary care setting is associated with an overall positive predictive value of up to 11.8% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 0.94-1.5% reported by two other studies in men only (N = 621321). The positive predictive values of change in bowel habit for colorectal cancer also appears to increase with age in men (2 studies, N = 71315) and in women (2 studies, N = 71315). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 3, 6-8).

Change in bowel habit (3 studies, N = 621601) presenting in a primary care setting is associated with an overall positive predictive value of up to 14% for colorectal cancer in a very small study (N = 280) in selected patients that contrasts with the estimates of 2.8% and 2.9% reported by two other studies in men only (N = 621321). The positive predictive values of change in bowel habit for colorectal cancer also appears to increase with age in men (2 studies, N = 71315) and in women (2 studies, N = 71315). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 3, 7-8).

Weight loss (4 studies, N = 44431) presenting in a primary care setting is associated with an overall positive predictive value of up to 3% for colorectal cancer which tended to increase with age (1 study, N = 2093) both in men (1 study, N = 43791) and in women (1 study, N = 43791). All the studies were associated with ≤ 3 bias or applicability concerns (see also Tables 1-3, 6-8).

Dyspepsia (3 studies, N = 4476) presenting in a primary care setting is associated with an overall positive predictive value of 0.6% for colorectal cancer. All the studies were associated with 1 applicability concerns (see also Table 3).

Other single symptoms (8 studies, N = 1245637) presenting in a primary care setting are associated with overall positive predictive values of up to 13.2% for colorectal cancer, but this estimate comes from a small study (N = 280) of selected patients and may therefore be inflated. All the studies were associated with ≤ 3 bias or applicability concerns (see also Table 3).

Rectal bleeding presenting with other symptoms (9 studies, N = 5770) in a primary care setting are associated with overall positive predictive values ranging from 0-100%, but many of these estimates are artificially inflated due to small numbers of patients in the calculations. All the studies were associated with ≤ 2 bias or applicability concerns (see also Table 4).

Other symptom combinations (2 studies, N = 3494) presenting in a primary care setting are associated with overall positive predictive values for colorectal cancer ranging from 0% for dyspepsia with dysphagia or jaundice to 13.51% for dyspepsia and anaemia. Both studies were associated with 1 bias/applicability concern (see also Table 5).
### Evidence tables

**Bellentani (1990)**

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th><strong>A. risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective consecutive patient series</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

- **Patient characteristics and setting**
  
  N = 254 (103 males/151 females); mean (SD) age of patients = Not reported; N = 140 were studied in primary care, N = 114 were referred to the gastroenterology services. It is unclear from the publication whether the patients who were referred to secondary care were a subset of “254 consecutive patients who presented to their GP during the study period for chronic abdominal pain” or whether they are recruited directly from secondary care (see Inclusion criteria).

  **Inclusion criteria:** All consecutive patients consulting 14 GPs of the local health district, taking care of 14000 citizens, or referred to the outpatient clinic of the Gastroenterology Unit, either complaining of recurrent abdominal pain or having intestinal problems (as judges by the GP), between January 1987 and March 1988.

  **Exclusion criteria:** Patients with acute abdomen, acute gastroenteritis or a clear cut diagnosis of upper gastrointestinal tract disease (gastitis, oesophagitis, peptic ulcer, or dyspepsia).

  **Clinical setting:** Primary/secondary care, Italy.

  Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

- **Index test**
  
  Recurrent abdominal pain or intestinal problems (as judges by the GP; not further specified)

  Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

  **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

#### B. Concerns regarding applicability

- **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Unclear concern |

### REFERENCE STANDARD

#### A. Risk of bias

- **Reference standard(s)**
  
  Double-contrast barium enema or colonoscopy no more than 2 months after the enrolment in the study.

  Is the reference standard likely to correctly classify the target condition? | Yes |
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without</td>
<td>Unclear (but all patients had a positive index test)</td>
</tr>
<tr>
<td>knowledge of the results of the index tests?</td>
<td></td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation</td>
<td>Low risk</td>
</tr>
<tr>
<td>have introduced bias?</td>
<td></td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the</td>
<td>Low concern</td>
</tr>
<tr>
<td>reference standard does not match the question?</td>
<td></td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for in the results but the number of true negatives and false negatives could not be ascertained from the reported results.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference</td>
<td>Yes</td>
</tr>
<tr>
<td>standard?</td>
<td></td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>NOTES</td>
<td></td>
</tr>
<tr>
<td>Collins (2012)</td>
<td></td>
</tr>
<tr>
<td>PATIENT SELECTION</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Retrospective patient series using the THIN database.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>A total of 2135540 patients were identified from 364 practices.</td>
</tr>
<tr>
<td>Symptoms:</td>
<td></td>
</tr>
<tr>
<td>Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain</td>
<td></td>
</tr>
<tr>
<td>(N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481</td>
<td></td>
</tr>
<tr>
<td>men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women),</td>
<td></td>
</tr>
<tr>
<td>anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men</td>
<td></td>
</tr>
<tr>
<td>only, N = 1670).</td>
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</tr>
<tr>
<td>Incident cases of colorectal cancer during the 2-year follow up period:</td>
<td></td>
</tr>
<tr>
<td>N = 3712 (2036 men, 1676 women).</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: Patients aged 30–84 years and registered with</td>
<td></td>
</tr>
<tr>
<td>practices between 1 January 2000 and 30 June 2008. Entry to the cohort</td>
<td></td>
</tr>
<tr>
<td>was defined as the latest of the study start date; the date the</td>
<td></td>
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<tr>
<td>patient registered with the practice; and for those patients with</td>
<td></td>
</tr>
<tr>
<td>red flag symptoms (see below), the date of the first recorded onset</td>
<td></td>
</tr>
<tr>
<td>within the study period.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients without a postcode-related Townsend score,</td>
<td></td>
</tr>
<tr>
<td>patients with a history of colorectal cancer at baseline, and patients</td>
<td></td>
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<tr>
<td>with a recorded ‘red-flag’ symptom in the 12 months prior to the study</td>
<td></td>
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<tr>
<td>entry date.</td>
<td></td>
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<tr>
<td>Clinical setting: Primary care, UK</td>
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<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
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<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>‘Red-flag’ symptoms: Rectal bleeding, loss of appetite, weight loss, abdominal pain, change in bowel habit (men only), and anaemia.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>2-year follow up</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
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<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients seem to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>The is very large, if not complete, overlap of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)</td>
</tr>
</tbody>
</table>

**Droogendijk (2011)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective peripheral hospital laboratory database study serving 265 GPs in Dordrecht (Holland).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 287; 129 men, 158 women; median (range) age = 70 (19-87) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: All women aged &gt; 50 years and all men aged ≥ 18 years who between January 2004 and December 2005 were diagnosed with iron-deficiency anaemia (haemoglobin &lt; 13.7 g/dl in men and &lt; 12.1 g/dl in women, and a serum ferritin level &lt; 25 µg/l for men and &lt; 20 µg/l for women).</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with a known history of iron-deficiency anaemia in the previous 2 years, a history of gastrointestinal malignancy or congenital haemoglobinopathy.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Holland</td>
<td></td>
</tr>
</tbody>
</table>

#### Are there concerns that the included patients and setting do not match the review question?

<table>
<thead>
<tr>
<th>Index test</th>
<th>New onset iron-deficiency anaemia (haemoglobin &lt; 13.7 g/dl in men and &lt; 12.1 g/dl in women, and a serum ferritin level &lt; 25 µg/l for men and &lt; 20 µg/l for women).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Endoscopy and 12-month follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

#### FLOW AND TIMING

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>It is unclear if all patients are accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>
In addition to the 24 patients with colorectal cancer, 3 patients had gastric cancer, 1 patient had oesophageal cancer and 1 patient had locally invasive endometrial cancer.

### Du Toit (2006)

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>10-year prospective consecutive patient sample from a rural UK GP practice (four doctors and 1 registrar; mean list size 4426 patients over the decade).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 265; age: 45-54 years: N = 51; 55-64 years: N = 75; 65-74 years: N = 63; ≥ 75 years: N = 76.</th>
</tr>
</thead>
</table>

- Inclusion criteria: Patients aged ≥ 45 years reporting new onset rectal bleeding with or without diarrhoea, during a 10-year period.
- Exclusion criteria: None listed

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Primary care, UK</th>
</tr>
</thead>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Low concern |

#### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>New onset rectal bleeding</th>
</tr>
</thead>
</table>

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Rigid sigmoidoscopy with barium enema or flexible sigmoidoscopy or colonoscopy.</th>
</tr>
</thead>
</table>

| Is the reference standard likely to correctly classify the target condition? | Yes |

| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |

| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |
### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### NOTES

13/265 patients had adenoma and 15/265 had colorectal cancer. 2/15 patients with cancer and 4/13 patients with adenoma had diarrhoea.

---

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 19 GPs in 3 practices (1 in each of the following: market town/rural community, suburban area and inner-city).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

- **Patient characteristics and setting**
  - N = 319 (143 males/176 females); mean (range) age of male patients = 56 (35-84) years, mean (range) age of female patients = 62 (35-84) years. Patients accepting a flexible sigmoidoscopy: 219/319; patients filling out questionnaire: 47/319; patients declining both sigmoidoscopy and questionnaire: 57/319. 61/219 patients had either a barium-enema (37) or a colonoscopy (24).
  - **Inclusion criteria**: GPs were asked to identify patients (aged > 34 years) whose primary complaint was rectal bleeding and those with other lower gastrointestinal symptoms who, on questioning, also had rectal bleeding. The patients were asked if they were willing to fill out a postal questionnaire and/or accept a flexible sigmoidoscopy.
  - **Exclusion criteria**: None listed.
  - **Clinical setting**: Primary care, UK.

- **Are there concerns that the included patients and setting do not match the review question?** Low concern

---

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Rectal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>interpretation differ from the review question?</strong></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Flexible sigmoidoscopy/barium enema/colonoscopy and follow up</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for and included in the results for rectal bleeding alone. However, for the analyses based on other symptoms presenting with rectal bleeding only those patients who received flexible sigmoidoscopy (N = 219) or who filled in a patient questionnaire (N = 47) were included.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>No</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td></td>
</tr>
<tr>
<td>Farrus Palou (2000)</td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Retrospective consecutive patient series from urban general practice covering a population of 24000.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 87 of whom the data from 29 were unavailable as no etiological diagnosis was found (due to patient refusal of further investigation [?; 8], lost to follow up [7], patient deterioration rendering them unsuitable for further investigation [14]); of the remaining 58 patients there were 14 males, 44 females; mean? (SD?) age = 54.26 (19.95) years.</td>
</tr>
<tr>
<td>Inclusion criteria: Patients aged &gt; 14 years who attended the health centre between 1 October 1995 and 31 September 1996 who were found to have new onset (previously unknown) anaemia (haemoglobin &lt; 13 g/dl for men</td>
<td></td>
</tr>
</tbody>
</table>
Exclusion criteria: Pregnant women.
Clinical setting: Spanish GP

<table>
<thead>
<tr>
<th>Question</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Anaemia (haemoglobin &lt; 13 g/dl for men and 12 g/dl for women)</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up I think</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>No diagnosis available for 29/87 patients</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td></td>
</tr>
<tr>
<td>This paper is published in Spanish</td>
<td></td>
</tr>
</tbody>
</table>

Fijten (1995)

<table>
<thead>
<tr>
<th>Question</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective consecutive patient series</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

Suspected Cancer: Appendix F (June 2015)  Page 536 of 1735
### Patient characteristics and setting

N = 269 (118 males/151 females), mean (SD, range) age = 42 (15, 18-75). Mean (SD) follow up time = 20 (5) months. For 51% rectal bleeding was the main reason for the encounter, and 49% had another reason (e.g., abdominal complaints), but blood loss per rectum was seen and mentioned by the patients. N = 8 used anticoagulants.

**Inclusion criteria:** From September 1988 to April 1990, patients with rectal bleeding were recruited by 83 GPs in Limburg, with an average duration of participation of 11 months per doctor. Patients were included when overt rectal bleeding was the reason for encounter or when there was a history of recent (within the previous three months) rectal blood loss visible for the patient.

**Exclusion criteria:** Aged below 18 or above 75 years, pregnancy, urgent admission to hospital (for, e.g., a massive bleeding or acute abdominal pain), and if follow-up data were not available.

**Clinical setting:** Primary care, Netherlands

### Concerns regarding applicability

#### Patient characteristics and setting

- **Are there concerns that the included patients and setting do not match the review question?** Unclear concern

### INDEX TEST

#### A. Risk of bias

- **Risk of bias**
  - Rectal bleeding
  - Were the index test results interpreted without knowledge of the results of the reference standard? Yes

#### B. Concerns regarding applicability

- **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

#### A. Risk of bias

- **Risk of bias**
  - Follow up for min 1 year.

#### B. Concerns regarding applicability

- **Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

### FLOW AND TIMING

#### A. Risk of bias

- **Flow and timing**
  - A total of 290 patients were recruited, however 21/290 were excluded as they were lost to follow-up (moved to an unknown destination).

- **Was there an appropriate interval between index test and reference standard?** Unclear
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

Hallissey (1990)

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling: Prospective consecutive patient series from a group of 10 general practices in England.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Patient characteristics and setting: N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.

Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia

Exclusion criteria: None listed.

Clinical setting: Primary care, England.

Are there concerns that the included patients and setting do not match the review question? Unclear concern

**INDEX TEST**

**A. Risk of bias**

Index test: Dyspepsia of any degree

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

**REFERENCE STANDARD**

**A. risk of bias**

Reference standard(s): Upper gastrointestinal endoscopy within 4 weeks and follow up.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**
<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>2659 patients were seen and 2585 attended for investigation</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).</td>
</tr>
</tbody>
</table>

Hamilton (2005)

| **PATIENT SELECTION** |  |
| **A. risk of bias** |  |
| Patient sampling | Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK. |
| Was a consecutive or random sample of patients enrolled? | No |
| Was a case-control design avoided? | No |
| Did the study avoid inappropriate exclusions? | Yes |
| For diagnostic case-control studies: |  |
| Attempts were made within the design or analysis to balance the comparison groups for potential confounders? | Yes |
| For diagnostic case-control studies: |  |
| The groups were comparable at baseline, including all major confounding and prognostic factors? | Yes |
| Could the selection of patients have introduced bias? | High risk |
| **B. Concerns regarding applicability** |  |
| Patient characteristics and setting | Cases: N = 349 (177 males/172 females), age at diagnosis: < 60 years: N = 45, 60-69 years: N = 97, 70-79 years: N = 113, 80+ years: N = 94. 210/349 had tumours at or distal to the splenic flexure, and 126/349 had tumours proximal to the splenic flexure, the remaining 13/349 has tumours in multiple or unknown sites. Duke’s staging was known for 305/349: 170/305 were Duke’s A or B, and 135/305 were Duke’s C or D. Controls: N = 1744 (885 males/859 females), age at diagnosis: < 60 years: N = 225, 60-69 years: N = 487, 70-79 years: N = 555, 80+ years: N = 477. |
| Inclusion criteria: | Cases: All patients aged ≥ 40 years with a primary colorectal cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer |
Controls: Five controls were matched to each case on sex, general practice, and age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case.

Exclusion criteria:
Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous colorectal cancer; or residence outside Exeter at the time of diagnosis.

Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**
Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

For diagnostic case-control studies:
Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

Reference standard(s) Colorectal cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

Flow and timing All the patients are accounted for.

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>
### PATIENT SELECTION

#### A. risk of bias

**Patient sampling**
Matched case-control study using patients in the Health Improvement Network (THIN), which uploads electronic medical records from GP practices using the VISION computer system. The records contain patient characteristics, all consultations, diagnoses, and primary care investigations. The database has 2.2 million currently active patients in over 300 practices; 4.7 million patients when historical data are included. Laboratory results have been transmitted electronically to most practices from the year 2000.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

**Cases:**
6442 cases of colorectal cancer (3421 men, 3021 women) of whom 3183 cases (1604 males, 1579 females) had a haemoglobin value measured in the year before the index date. Age of patients with a haemoglobin estimation: 30-59 years: N = 489; 60-69 years: N = 748; 70-79: N = 1085; 80+ years: N = 861. The haemoglobin results were taken in a median interquartile range of 62 (28-122) days before the index date. A mean cell volume (MVC) result was available in 2951 cases of which 764 results showed microcytosis. Ferritin results were available for 723 and 353 of these were low.

- Haemoglobin > 12.9 g dl\(^{-1}\): Men/women (N = 805/459);
- Haemoglobin 12-12.9 g dl\(^{-1}\): Men/women (N = 203/289);
- Haemoglobin 11-11.9 g dl\(^{-1}\): Men/women (N = 171/238);
- Haemoglobin 10-10.9 g dl\(^{-1}\): Men/women (N = 129/226);
- Haemoglobin 9-9.9 g dl\(^{-1}\): Men/women (N = 118/146);
- Haemoglobin < 9 g dl\(^{-1}\): Men/women (N = 178/221)

**Controls:**
45066 matched controls were available, of whom 10514 controls (5223 males, 5291 females) had a haemoglobin value measured in the year before the index date. Age of patients with a haemoglobin estimation: 30-59 years: N = 1158; 60-69 years: N = 2215; 70-79: N = 3823; 80+ years: N = 3318. Haemoglobin results were taken in a median interquartile range of 134 (59-235) days before the index date. AN MVC result was available in 9648 controls of which 210 results showed microcytosis. Ferritin results were...
available for 825 and 129 of these were low.
Haemoglobin > 12.9 g dl\(^{-1}\): Men/women (N = 4131/2992);
Haemoglobin 12-12.9 g dl\(^{-1}\): Men/women (N = 572/1337)
Haemoglobin 11-11.9 g dl\(^{-1}\): Men/women (N = 293/616)
Haemoglobin 10-10.9 g dl\(^{-1}\): Men/women (N = 131/225)
Haemoglobin 9-9.9 g dl\(^{-1}\): Men/women (N = 49/85)
Haemoglobin < 9 g dl\(^{-1}\): Men/women (N = 47/36)

**Inclusion criteria:**
Cases: All patients with colorectal cancer were identified, who were aged 30 years or older, and diagnosed between January 2000 and July 2006. All participants had at least 2 years of electronic records prior to the date of diagnosis of the case (the index date).
Controls: Up to seven controls were randomly selected for each case, using a computerised random numbers sequence. Controls were free from colorectal cancer and were matched for practice, sex, and age. Where possible controls were born in the same year as cases, if none were available within 1 year of the cases, the range was expanded to 2 years, continuing to a maximum of 5 years. All participants had at least 2 years of electronic records prior to the date of diagnosis of the case (the index date).

**Exclusion criteria:** None listed.

**Clinical setting:** Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Haemoglobin results were taken in the year before the index dates were studied. If more than one haemoglobin measurement had been taken, the final value was used for analysis. MCV and ferritin results for the same year were also collated. Microcytosis was defined as an MCV &lt; 80.0 fl, and a low ferritin as &lt; 20 ng ml(^{-1}).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

**For diagnostic case-control studies:**

<table>
<thead>
<tr>
<th>Investigators were kept 'blind' to other important confounding and prognostic factors?</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Could the conduct or interpretation of the index test have introduced bias?**

| Low risk |
|---|---|

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Colorectal cancer code in the THIN database.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

**Could the reference standard, its conduct, or its**

| Low risk |
|---|---|
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Type of Bias</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>The MVC and ferritin data was not available for all included cases and controls, which may bias the results reported for the combined haemoglobin + iron deficiency estimates.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### NOTES

The is very large, if not complete, overlap of the data used in this study with those used in Collins (2012) and Hamilton (2009)

### Hamilton (2009)

#### A. risk of bias

<table>
<thead>
<tr>
<th>Type of Bias</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Matched case-control study using patients in the Health Improvement Network (THIN), which uploads electronic medical records from GP practices using the VISION computer system. The records contain patient characteristics, all consultations, diagnoses, and primary care investigations. The database has 2.2 million currently active patients in over 300 practices; 4.7 million patients when historical data are included. Laboratory results have been transmitted electronically to most practices from the year 2000.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5477 cases of colorectal cancer from 317 practices (2911 men, 2566 women); median (inter-quartile range) age at diagnosis: 72 (63-79) years. Constipation: N = 1477/27%; Diarrhoea: N = 988/18%; Change in bowel habit: N = 615/11.2%; Rectal bleeding: N = 853/15.6%; Weight loss 5-9.9%: N = 210/3.8%; Weight loss ≥ 10%: N = 351/6.4%; Abdominal pain: N = 1629/29.7%; Haemoglobin &lt; 12 g dl⁻¹: N = 1424/26%; Mean red cell volume &lt; 80 fl: N = 363/6.6%; Irritable bowel syndrome: N = 135/2.5%; Diabetes: N =</td>
<td></td>
</tr>
</tbody>
</table>
626/11.4%; Obesity: N = 510/9.3%.

**Controls:**
38314 matched controls (with only seven very elderly cases having fewer than seven controls available). 36925 (96.4%) controls were matched to the same year of birth, and 1150 to the adjoining year, leaving only 239 controls 2 to 5 years different in age.

Constipation: N = 4051/10.6%; Diarrhoea: N = 2171/5.7%; Change in bowel habit: N = 375/1%; Rectal bleeding: N = 460/1.2%; Weight loss 5-9.9%: N = 852/2.2%; Weight loss ≥ 10%: N = 678/1.8%; Abdominal pain: N = 3121/8.1%; Haemoglobin < 12 g dl⁻¹: N = 1803/4.7%; Mean red cell volume < 80 fl: N = 923/2.4%; Irritable bowel syndrome: N = 325/0.8%; Diabetes: N = 3679/9.6%; Obesity: N = 3510/9.2%.

**Inclusion criteria:**
Cases: All patients with colorectal cancer were identified, who were aged 30 years or older, and diagnosed between January 2001 and July 2006. All participants had at least 2 years of electronic records prior to the date of diagnosis of the case (the index date).

Controls: Up to seven controls were randomly selected for each case, using a computerised random numbers sequence. Controls were free from colorectal cancer and were matched for practice, sex, and age. Where possible controls were born in the same year as cases, if none were available within 1 year of the cases, the range was expanded to 2 years, continuing to a maximum of 5 years. All participants had at least 2 years of electronic records prior to the date of diagnosis of the case (the index date).

**Exclusion criteria:** None listed.

**Clinical setting:** Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>From a review of the literature, 23 candidate variables (features) were identified, either a symptom, or an abnormal primary care investigation, or a predisposing risk marker such as obesity. Codes for irritable bowel syndrome as a potential misdiagnosis were also identified. For some symptoms the availability of data on related prescriptions were also used, for example, prescriptions for antidiarrhoeals and laxatives were obtained as possible surrogates for the relevant symptoms, and similarly antispasmodic drugs for irritable bowel syndrome. Features were designated as new if there were no similar symptoms or prescriptions observed previously in the 2 years before the index date. Weight loss was calculated from the change between the last recorded weight and the highest weight in the previous 2 years, separated into two categories: ≥ 10% weight loss or 5-10% weight loss. Patients were assigned to their maximum weight loss category. Obesity was defined as a body mass index &gt; 30 kg/m² within 2 years of the index date. Diabetes was considered to be present if it had ever been diagnosed. &lt; 2.5% cases or controls had an abnormal rectal examination (15 cases, 2 controls), abdominal masses (86 cases, 19 controls), a positive FOB (7 cases, 2 controls), or thrombo-embolism (24 cases, 74 controls), and these features were therefore not analysed any further.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge</td>
<td>Yes</td>
</tr>
</tbody>
</table>
of the results of the reference standard?

<table>
<thead>
<tr>
<th>For diagnostic case-control studies:</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Low risk</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Colorectal cancer code in the THIN database.</th>
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<tr>
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</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
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<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the participants are accounted for in the results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

The is very large, if not complete, overlap of the data used in this study with those used in Collins (2012) and Hamilton (2008, for anaemia)

### Heikkinen (1995)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Consecutive patient series from 11 GPs (from 3 rural health centres) and from the catchment area of 6 physicians in the health centre of an urban area (population [individuals &gt; 14 years old] of study area = 24600) in Finland.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient | N = 400; 152 males, 248 females; 77% were > 44 years. |
**Inclusion criteria**: Consecutive patients who consulted their GP from January 11th 1993 to January 12th 1994 for dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

**Exclusion criteria**: Patients with symptoms of an acute condition within the abdomen or who had had an upper intestinal endoscopy performed within the last 3 months or aged < 15 years.

**Clinical setting**: Primary care, Finland.

---

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

---

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Low concern

---

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy, upper abdominal ultrasound, more detailed interview, blood count, serum screening (creatinine, alkaline phosphatise, alanine aminotransferase, amylase, and C-reactive protein), lactose intolerance test, and follow up of ≥ 1 month.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

---

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

In total N = 9 had cancer: 0 colorectal, 2 oesophageal and 7 stomach (of which 3 were lymphomas of the MALT type (Mucosa-associated lymphoid...
Heintze (2005)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | N = 422 (222 males/199 females); aged < 50 years: N = 153, aged ≥ 50 years: N = 268. The most common accompanying symptoms associated with rectal bleeding were: Abdominal pain > 3 weeks (N = 97), change in bowel habit > 3 weeks (N = 73), anaemia (N = 23), and weight loss (N = 13). |

**Inclusion criteria:** Patients aged ≥ 15 years presenting with ≥ 1 bowel symptom to one of the participating 116 GP. The present analyses only included patients who presented with the first sign of rectal bleeding and associated symptoms, but without any pre-existing bowel diseases.

**Exclusion criteria:** ≤ minimum level of data entry for each patient by the participating physician.

**Clinical setting:** Primary care, Germany.

| Are there concerns that the included patients and setting do not match the review question? | Low concern |

### INDEX TEST

#### A. Risk of bias

| Index test | Rectal bleeding, abdominal pain > 3 weeks, change in bowel habit > 3 weeks, anaemia, and weight loss. |

| **Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes |

| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

| Reference standard(s) | A number of different diagnostic investigations, although some patients did not undergo any, - their explanatory notes were examined instead |

| **Is the reference standard likely to correctly classify the target condition?** | Unclear |

| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear (but all patients had a positive index test) |

| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |
B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>93 patients did not undergo any investigations, and in 22/93 the course of disease and the diagnostics could not be assessed with the data provided in the explanatory notes. The results are therefore only reported for the 400 patients for whom the data are known</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>No</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**NOTES**

Over the course of 1 year, 2239 patients with chronic bowel symptoms and diseases were registered by 116 participating GPs. 24/116 GPs withdrew from the study before study completion (due to personal reasons (12) or lack of cooperation (10)), leaving 1696 patients registered by 94 GPs of whom 1584 met the minimum requirements for inclusion. 422/1584 patients presented with rectal bleeding.

**Helfand (1997)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive patient series from the walk-in and general medical clinics of the Veterans Affairs Medical Center, Palo Alto, California.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
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<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 201; 200 males, 1 female; mean ages (SD; 3 values given based on final diagnostic category): “None” (N = 49) = 53.8 (15.4) years; “anorectal” (N = 104) = 54.6 (13.6) years; “serious” (N = 48) = 58.3 (11.3) years.</th>
</tr>
</thead>
</table>

**Inclusion criteria:** Patients who between January 1981 and October 1983 presented to the walk-in and general medical clinics of the Veterans Affairs Medical Center, Palo Alto, California were given a questionnaire after by the nursing personnel after their vital signs had been measured. Patients who according to their answers had experienced rectal bleeding within the last 3 months and not sought medical attention for it were invited to take part in the study.

**Exclusion criteria:** Patients with no data available at 6 and 12 months follow up.

**Clinical setting:** Walk-in and general medical clinics of the Veterans Affairs Medical Center, Palo Alto, California

| Are there concerns that the included patients and setting | High concern |
## INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>New onset (within 3-months) rectal bleeding (blood in stool or on toilet paper)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Were the index test results interpreted without knowledge of the results of the reference standard? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Could the conduct or interpretation of the index test have introduced bias? <strong>Low risk</strong></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

## REFERENCE STANDARD

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up 6-12 months and examination of medical records 8-10 years after study entry.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Is the reference standard likely to correctly classify the target condition? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests? <strong>No</strong></td>
</tr>
<tr>
<td></td>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias? <strong>Low risk</strong></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the review question? | Low concern |

## FLOW AND TIMING

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Was there an appropriate interval between index test and reference standard? <strong>Unclear</strong></td>
</tr>
<tr>
<td></td>
<td>Did all patients receive the same reference standard? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Were all patients included in the analysis? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Could the patient flow have introduced bias? <strong>Low risk</strong></td>
</tr>
</tbody>
</table>

## NOTES

The authors mention that between 2 and 10 years after study entry 3 patients developed colorectal cancer. These patients do not appear to be included as true positives.

---

**Hippisley-Cox (2012)**

## PATIENT SELECTION

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Was a consecutive or random sample of patients enrolled? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Was a case-control design avoided? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Did the study avoid inappropriate exclusions? <strong>Yes</strong></td>
</tr>
<tr>
<td></td>
<td>Could the selection of patients have introduced bias? <strong>Low risk</strong></td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

| Patient characteristics and setting | A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).
| **Symptoms:** | **Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821).**
| Incident cases of colorectal cancer during the 2-year follow up period: | N = 2603 (1562 colon and 1041 rectum).
| **Inclusion criteria:** | All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.*
| **Exclusion criteria:** | Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.
| **Clinical setting:** | Primary care, UK

### Are there concerns that the included patients and setting do not match the review question?
Low concern

### INDEX TEST

#### A. Risk of bias

| Index test | ‘Red-flag’ symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months).
| **Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk

### B. Concerns regarding applicability

| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern

### REFERENCE STANDARD

#### A. Risk of bias

| Reference standard(s) | 2-year follow up
| **Is the reference standard likely to correctly classify the target condition?** | Yes
| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear

---
### Could the reference standard, its conduct, or its interpretation have introduced bias?

| Low risk |

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? |

| Low concern |

### FLOW AND TIMING

| A. risk of bias |

#### Flow and timing

A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

| Was there an appropriate interval between index test and reference standard? |

| Yes |

| Did all patients receive the same reference standard? |

| Yes |

| Were all patients included in the analysis? |

| No |

| Could the patient flow have introduced bias? |

| Low risk |

### NOTES

Please note there is some overlap between this patient sample and that of Parker (2007)

### Jones (2007)

### PATIENT SELECTION

| A. risk of bias |

#### Patient sampling

Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.

| Was a consecutive or random sample of patients enrolled? |

| Yes |

| Was a case-control design avoided? |

| Yes |

| Did the study avoid inappropriate exclusions? |

| Yes |

| Could the selection of patients have introduced bias? |

| Low risk |

### B. Concerns regarding applicability

| Patient characteristics and setting |

| A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years. Number of first occurrences in patients with no previous diagnosis of cancer: Haematuria: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females. Haemoptysis: N = 4822, mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: N = 10. Sex (of final sample): 2930 males, 1882 females. Dysphagia: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females. |
Rectal bleeding: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females.

Inclusion criteria: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.

Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

| **REFERENCE STANDARD** | |
| **A. risk of bias** | |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear (but all patients had a positive index test) |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |
| **B. Concerns regarding applicability** | |
| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |
### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for in the results.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates. Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:

- **Haematuria**: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.
- **Dysphagia**: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men.

*Estimates based on the pre-specified cancers may be thus conservative for these symptoms.*

- **Haemoptysis**: Extension of the diagnostic criteria yielded 6 additional cancers.
- **Rectal bleeding**: Extension of the diagnostic criteria yielded 2 additional cancers.

---

### Lawrenson (2006)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Database study using patients from a sample of UK practices contributing data to the General Practice Research Database.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
</table>
| Patient characteristics and setting | Anaemia cases: N = 67164 (18896 males, 48268 females)  
Changes in bowel habit cases: N = 27524 (10934 males, 16590 females)  
Rectal bleeding cases: N = 44741 (21472 males, 23269 females)  
Colorectal cancer cases: N = 9143 |

Inclusion criteria: All patients aged 40-89 years presenting to their GP between 1 January 1992 and 31 December 1999 with new symptoms of anaemia, change in bowel habit or rectal bleeding, who had ≥ 1 year of data.
Exclusion criteria: Patients with colorectal cancer, or a diagnosis of colorectal...
cancer within 1 year of presentation.
Clinical setting: Primary care, UK.

| **Are there concerns that the included patients and setting do not match the review question?** | Low concern |
| **INDEX TEST** |  |
| **A. Risk of bias** |  |
| **Index test** | Anaemia, change in bowel habit or rectal bleeding as identified by their diagnostic codes |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| **B. Concerns regarding applicability** |  |
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

| **REFERENCE STANDARD** |  |
| **A. risk of bias** |  |
| Reference standard(s) | Follow up from presenting symptom until diagnosis of colorectal cancer, death or the end of the patient record. |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |
| **B. Concerns regarding applicability** |  |
| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

| **FLOW AND TIMING** |  |
| **A. risk of bias** |  |
| Flow and timing | All patients appear to be accounted for |
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes (probably) |
| Could the patient flow have introduced bias? | Low risk |

| **NOTES** |  |
| The authors state that the positive predictive values were derived from Kaplan-Maier curves constructed for men and women for each symptom cohort in 10-year age bands and report the positive predictive values of colorectal cancer being diagnosed within 12 months of initial symptoms per 100 patients presenting. It is unclear to me why this method was chosen over just calculating the values by dividing the true positives by the total positives and how if these calculations differ from those of the other studies. The raw data is not presented and these data can therefore not be included in the meta-analysis. |  |

Lucas (1996)
**PATIENT SELECTION**

### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective laboratory database (recording all full blood counts analysed in the district) study from one UK health district (population 290000).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Patient characteristics and setting | N = 130 of whom 21 were clearly attributable to non-gastrointestinal disease (e.g., urinary tract bleeding, uterine/respiratory/surgical blood loss and sideroblastic anaemia). In the remaining 109 patients with a presumed gastrointestinal cause N = 29 were aged < 65 years, N = 51 were aged 65-79 years and N = 29 were aged > 80 years. |

| Inclusion criteria: Women aged > 50 years and all men who between October 1991 and March 1992 were found to have probable iron-deficiency anaemia (haemoglobin < 11 g/dl in women and < 12 g/dl in men, and men cell volume < 83 fl) where the date of the first abnormal full blood count fell either within or 3 months prior to the study period and where there had been no other episode of anaemia within the previous 2 years. |
| Exclusion criteria: None listed. |
| Clinical setting: UK primary and beyond |

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

### A. Risk of bias

| Index test | New onset iron-deficiency anaemia. Hypochronic microcytic anaemia was presumed to be due to iron-deficiency anaemia unless proven otherwise through appropriate investigation. |

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

### A. risk of bias

| Reference standard(s) | Follow up using hospital and general practice records until 18 months after study period finish. |

| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |

### B. Concerns regarding applicability

| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### NOTES

In addition to the 9 patients with colorectal cancer, 5 patients had gastric cancer.

---

### Mant (1989)

#### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective consecutive patient series from 58 general practitioners in New South Wales, Australia.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 145; 77 males, 68 females; mean age (SD, range) = 57.7 (11.9, 40-95) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: All patients aged ≥ 40 years who consulted the GP with rectal bleeding.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients (1) for whom it was considered that their age or general medical condition precluded colonoscopy, (2) who were known to have inflammatory bowel disease, colorectal cancer or polyposis coli, (3) with a coagulation defect or haemalogic disorder, (4) where the bleeding was melenic, or (5) who refused investigation.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: General practice in New South Wales, Australia.</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

#### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>New onset (within 6-months) rectal bleeding (blood in stool or on toilet paper)</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Flexible sigmoidoscopy and air-contrast barium enema ± colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

In addition to the 15 patients with colorectal cancer, 1 patient had anal cancer and 1 patient had lymphoma of the ascending colon. Both of these are included in the meta-analyses, but only the lymphoma patient is included in the subgroup analyses reported by the authors.

Meineche-Schmidt (2002)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Consecutive patient series from 82 GPs in Denmark.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1491; 688 males, 803 females; age groups: 18-37 years: N = 377; 38-50 years: N = 369; 51-64 years: N = 338; 65+ years: N = 402.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Consecutive patients who consulted their GP between June 1991 and May 1993 for dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Primary care, Denmark.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>
### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>18 months-3 years and 10 months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

In total N = 31 had cancer: 17 colorectal, 8 gastro-oesophageal (no subgroup analyses presented for these patients) and 6 other.

Metcalf (1996)

### PATIENT SELECTION

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive patient sample from UK GPs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient | N = 99, 42 males, 57 females; median age (range) = 58 (40-86) years. |
**characteristics and setting**

| Inclusion criteria: Patients aged > 40 years presenting with rectal bleeding of recent onset (< 1 year). Exclusion criteria: Patients refusing colonoscopy. Clinical setting: Primary care, UK |

**Are there concerns that the included patients and setting do not match the review question?** Low concern

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th>Recent onset (&lt; 1 year) rectal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th>Colonoscopy ± barium enema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

| Muris (1993) |

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th>Prospective consecutive patient series from 11 general practitioners in Maastricht (Holland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 578; 212 males, 342 females; age groups: 18-39 years: N = 295; 40-49 years: N = 80; 50-59 years: N = 91; 60-75 years: N = 88.</td>
</tr>
<tr>
<td>Inclusion criteria: Patients who during a 3-month period consulted one of the participating GPs for abdominal complaints.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients aged &lt; 18 years and patients with a condition necessitating immediate referral or admission to hospital.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Holland</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td>INDEX TEST</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Abdominal complaints. Not further specified, but the authors do report that the duration of pain before the patient presented for the first time for the evaluation of abdominal pain varied from some days to more than 1 year.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up for 15 months.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
NOTES: Although not explicitly stated by the authors it is implied that the patients included were those presenting with the abdominal complaint for the first time.

---

Muris (1995)

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 80/460 general practitioners in Limburg (Holland)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 933; 335 males, 598 females; age range = 18-75, aged &gt; 30 years: N = 712, aged &gt; 40 years: N = 517, aged &gt; 60 years: N = 171.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>GPs in Holland</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? High concern

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>New abdominal complaints lasting ≥ 2 weeks. Not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or its interpretation differ from the review question? High concern

### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up for ≥ 12 months (mean = 18 months).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern
### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

#### NOTES

Other cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), kidney (1/933), cervix (1/933), other cancer of the female genital system (2/933), and other and unspecified sites (2/933).

Nørrelund (1996)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Patient characteristics and setting

| N = 417, but no demographic data reported for 45 patients who presented with similar rectal bleeding patterns to previously experienced rectal bleeding or for 8 patients with non-reported rectal bleeding pattern. The characteristics for the 364 patients with new onset or changed pattern rectal bleeding are as follows: 168 males, 196 females; age groups: 40-69 years: N = 254; 70-79 years: N = 85; 80+ years: N = 25. |

Inclusion criteria: Patients aged ≥ 40 years who between August 1989 and October 1992 presented to the participating GPs with rectal bleeding.

Exclusion criteria: Known inflammatory bowel disease, colonic polyps, polyposis coli, colorectal cancer, predisposition to haemorrhage, and melaena stool.

Clinical setting: Primary care, Denmark

Are there concerns that the included patients and setting do not match the review question? | Low concern |

### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
</tbody>
</table>

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

Could the conduct or interpretation of the index test have introduced bias? | Low risk |

#### B. Concerns regarding applicability
<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up (range = 22-57 months)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>NOTES</td>
<td></td>
</tr>
<tr>
<td>Oudega (2006)</td>
<td></td>
</tr>
<tr>
<td>PATIENT SELECTION</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in Holland.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years.</td>
</tr>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, Holland.</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>
### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis.</th>
</tr>
</thead>
</table>

- **Were the index test results interpreted without knowledge of the results of the reference standard?** Yes
- **Could the conduct or interpretation of the index test have introduced bias?** Low risk

**B. Concerns regarding applicability**

- **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2 years follow up.</th>
</tr>
</thead>
</table>

- **Is the reference standard likely to correctly classify the target condition?** Yes
- **Were the reference standard results interpreted without knowledge of the results of the index tests?** No
- **Could the reference standard, its conduct, or its interpretation have introduced bias?** Low risk

**B. Concerns regarding applicability**

- **Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

### FLOW AND TIMING

**A. Risk of bias**

- **Flow and timing** All patients appear to be accounted for
- **Was there an appropriate interval between index test and reference standard?** Yes
- **Did all patients receive the same reference standard?** Yes
- **Were all patients included in the analysis?** Yes
- **Could the patient flow have introduced bias?** Low risk

**NOTES** In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

### PATIENT SELECTION

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective 8-week study of patients presenting to 159 primary care physicians (approximately 63600 patient visits during the study period in total) in Italy.</th>
</tr>
</thead>
</table>

- **Was a consecutive or random sample of patients enrolled?** No
<table>
<thead>
<tr>
<th>Was a case-control design avoided?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 280; 120 males, 160 females; median age (range) = 61 (18-87) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP “with symptoms considered suspicious for the presence of a colon disease to rule out the presence of colorectal cancer” and who were investigated with a colonoscopy or double-contrast barium enema [The decision of how (colonoscopy or double-contrast barium enema) and when to investigate the colon was made only by the physicians on the basis of the clinical evaluation during the visit].</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with previous diagnoses of colorectal disorders or a recent large bowel examination.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, Italy.</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Abdominal pain, bloating, constipation, rectal bleeding, diarrhoea, iron-deficiency anaemia (haemoglobin levels &lt; 14 g/dl for males and &lt; 12 g/dl for females, in the presence of ferritin &lt; 30 µg/l and a median corpuscular value &lt; 80 fl), change in bowel habits (onset of diarrhoea or constipation or altered stool in the previous 3 months) and weight loss (decrease of ≥ 3 kg in the 3 months prior to the visit).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING
### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>56/332 patients were excluded due to lack of mandatory fields (age, sex, clinical history, presenting symptoms and procedure results) in the database (N = 35) or violation of exclusion criteria (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

### NOTES

Parker (2007)

#### PATIENT SELECTION

##### A. risk of bias

**Patient sampling**

Prospective patient series using patients in the QResearch database.

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Could the selection of patients have introduced bias?**

Low risk

#### B. Concerns regarding applicability

**Patient characteristics and setting**

Rectal bleeding: N = 29007 (13931, males, 15076 females); median age (inter-quartile range) = 54 (40-69) years.

Post-menopausal bleeding: N = 10122 (10122 females); median age (inter-quartile range) = 58 (54-67) years.

Inclusion criteria:

All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system before 1 April 1998 and had complete data up to 1 April 2005. Patients were included if they were registered with an eligible practice at any time between 1 April 1998 and 31 March 2003, had been registered with the practice for ≥ 12 months and had a first-ever consultation for rectal bleeding and were aged ≥ 25 years, or post-menopausal bleeding and were aged ≥ 40 years, between 1 April 1998 and 31 March 2003.

Exclusion criteria:

- Previous record of colorectal cancer (for patients presenting with rectal bleeding) and endometrial cancer (for patients presenting with post-menopausal bleeding)

**Clinical setting:** Primary care, UK

Are there concerns that the included patients and setting do not match the review question? Low concern

#### INDEX TEST

##### A. Risk of bias

**Index test**

First ever presentation of rectal bleeding, first ever presentation of post-menopausal bleeding.

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

#### B. Concerns regarding applicability


### Are there concerns that the index test, its conduct, or interpretation differ from the review question?

**Low concern**

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?

**Low concern**

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

Please note there is some overlap between this patient sample and that of Hippisley-Cox (2012).

### PATIENT SELECTION

#### A. risk of bias

Patient sampling | Prospective consecutive patient sample from UK GPs. |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Patient characteristics and setting | N = 604, 273 males, 331 females; median age (range) = 52 (18-97) years.  
Inclusion criteria: Patients who between September 1996 and June 1999 presented to the participating GPs with rectal bleeding.  
Exclusion criteria: Patients with ulcerative colitis, current warfarin treatment or missing data for the kind of bleeding.  
Clinical setting: Primary care, UK |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### INDEX TEST

#### A. Risk of bias
<table>
<thead>
<tr>
<th><strong>Index test</strong></th>
<th>Rectal bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up (min 4 years)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Deprivation categories were allocated to participants by mapping their postcodes with national deprivation categories (septiles) derived from the Carstairs scores generated by MIMAS at Manchester University using 1991 census data.</td>
</tr>
<tr>
<td>Stellon (1997)</td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective? consecutive patient series from semi-rural UK general practice with a patient list between 2400-3400 during the study period.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>N = 26; 5 males, 21 females; age range = 51-87 years.</td>
</tr>
</tbody>
</table>
Inclusion criteria: All patients aged > 50 years found to have iron deficiency anaemia between January 1989 and March 1994. Exclusion criteria: None listed. 
Clinical setting: UK GP

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Iron deficiency anaemia (&lt; 12 g/dl haemoglobin and/or mean corpuscular volume &lt; 80 fl with ferritin ≤ 16 ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up during 5 year study period.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Wauters (2000)

**PATIENT SELECTION**

**A. risk of bias**

<p>| Patient sampling | Prospective study of a network of sentinel Belgian general practices (covering 1% of the Belgian population) registering epidemiological data. |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Characteristics and Setting</th>
<th>N = 386; gender distribution not reported; age groups: &lt; 50 years: N = 141; 50-59 years: N = 57; 60-69 years: N = 71; 70-79 years: N = 66; ≥ 80 years: N = 51.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>All patients who in 1993-4 presented with rectal bleeding.</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>GPs in Belgium</td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index Test</th>
<th>Rectal bleeding (any blood of rectal origin on stool, underwear or toilet paper irrespective of duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or its interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>18-30 months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### Patient Selection

#### A. Risk of Bias

<table>
<thead>
<tr>
<th>Patient Sampling</th>
<th>Retrospective database study using the laboratory databases of two district general hospitals including all the general practices using these laboratories.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 431; 154 males, 277 females; median age (inter-quartile range) = 75 (65-81) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: All female patients aged &gt; 50 years and male patients aged &gt; 20, with haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10¹²/l between June 1997 and May 1998.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: History of anaemia within previous 12 months, known haematological abnormalities (e.g., haemoglobinopathy), unavailable notes at follow up. That is, patients with a history of cancer were not excluded.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: UK GP</td>
<td></td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### Index Test

#### A. Risk of Bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Iron deficiency anaemia (haemoglobin concentrations ≤ 110 g/l (women) or ≤ 120 g/l (men), and mean cell volume &lt; 82 fl (district 1) or 78 fl (district 2), and red cell count ≤ 5.5 x 10¹²/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### Reference Standard

#### A. Risk of Bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Minimum 3 years follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

FLOW AND TIMING

A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

In total N = 48 had gastrointestinal cancer (11 upper, 2 small bowel and 35 lower, including recurrent tumours) and N = 23 had non-gastrointestinal cancers, but the study only reports the type of some of these cancers (3 lung + 1 lung tumour secondary to a previous breast tumour, 1 ovary, 2 bladder, 1 Hodgkin's, 1 Non-Hodgkin's, 1 endometrial sarcoma, 1 lymphoma, 1 endometrial) and has therefore not been added to the evidence reviews for the non-gastrointestinal cancers. The paper considers both the lower gastrointestinal cancers and the small bowel cancers as colorectal cancer and in order to present subgroup analyses by gender I have maintained this grouping and not added this paper to the evidence review for small intestine.

References

Included studies


Panzuto, F., Chiriatti, A., Bevilacqua, S., Giovannetti, P., Russo, G., Impinna, S., Pistilli, F., Capurso, G., Annibale, B., Delle, Fave G., and Digestive and Liver Disease and Primary Care Medicine Lazio

Excluded studies (with excl reason)
Not in PICO
Guideline
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Mixed secondary care, primary care and screening; results cannot be extracted separately for primary care
424.

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Pre-1980

Not in PICO

Not in PICO

Pre-1980

Not in PICO

Not in PICO

Systematic review, but current review updates it

Not in PICO

Same as Halligan 2013

Not in PICO

Not in PICO

Not in PICO (referred population)

Not in PICO
Not in PICO
Narrative review
Pre-1980
Not in PICO
Not in PICO
Narrative review
Letter/narrative review
Not in PICO
Not in PICO
Not in PICO
Pre-1980
Not in PICO
Pre-1980
SR, but include 8 studies that are all included in this review


Borhan-Manesh, F. (2009) "Low caliber stool" and "pencil thin stool" are not signs of colo-rectal cancer. [Review] [30 refs]. *Digestive Diseases & Sciences*, 54: 208-211.
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Symptoms not linked with cancer, not patients presenting with symptoms unprompted (patients prompted to attend)

Narrative review

Not in PICO

Not in PICO

Not in PICO

Chan, K.-W., Ng, P. T. K., Chan, C., Ng, C.-L. & Yiu, Y.-K. (2009) The Family Medicine Specialist Surgical Clinic - A new project to benefit the patient, hospital specialist, family physicians and the private sector in the community. Hong Kong Practitioner, 31: 24-29.
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Sub-population of Hamilton (2005)

Pre-1980

Not in PICO

Pre-1980

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Gastroenterologica Latinoamericana, 41: 137-141.
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO (referred patients)
Narrative review/guideline
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Not in PICO

Not in PICO
Denters, M., Bossuyt, P. M., Deutekom, M., Fockens, P. & Dekker, E. (2011) Females, younger persons and persons with a negative family history more often have a false positive FIT result. Gastroenterology, 140: S418.

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO - Willie has requested we check this, so ordered now

Not in PICO

Pre-1980

Not in PICO

Case report

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Publication of data from Fijten 1995
"SR", but contain no data from primary care
Not in PICO
Not in PICO
Not in PICO
"SR", but majority of included studies are secondary care, the only relevant studies from primary care are already included
Narrative review
Not in PICO
Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO (referred population)


Not in PICO


Not in PICO


Not in PICO


Same data as Mant, but Mant's got other data too, so just include Mant


Pre-1980
Not in PICO
Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO.
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO (referred population)
Same as Halligan 2013
Narrative review
Review of studies already included
Narrative review
Data already included
Not in PICO
Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Does not distinguish between malignancy categories, but companion ref does, so that’s included instead.


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO


Comment

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Narrative review


SR, all PC studies included apart from one on haemoccult testing


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review


Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO (secondary care setting)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review

Same as Yates (2004)


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO (secondary care)


Not in PICO


Not in PICO


Symptoms not linked with cancers; analysis based on number of codes, not patients.
Symptoms not linked with cancers; analysis based on number of codes, not patients
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO

Not in PICO

Not in PICO (referred v asymptomatic population controls)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Comment
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Danish publication of same data as Noerrelund & Noerrelund already included in Astin et al.

Not in PICO

Pre-1980

Not in PICO

Not in PICO (referred population)

Not in PICO (secondary care setting)

Duplicate

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not relevant; cancer patients not symptomatic patients


Case report


Narrative review

Not in PICO


Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO (S&S: population; Tests: outcomes)

Not in PICO

Comment

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Comment/letter


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO (referred patients)


Not in PICO

error in medicine: Analysis of 583 physician-reported errors. Archives of Internal Medicine, 169: 1881-1887.


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Systematic review, but current review updates it


Not in PICO
Pre-1980
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not relevant; cancer patients not symptomatic patients

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Guideline


Narrative review


Guideline


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Systematic review, checked for relevant studies (Brenna 1990 [patients referred for colonoscopy, but not a diagnostic test accuracy study, i.e., outcomes not in PICO for tests and cannot be calculated], Farrands 1985 [referred patients], Zarchy 1991 [patients referred for barium enema, but not a diagnostic test accuracy study, i.e., outcomes not in PICO for tests])


Not in PICO


Not in PICO


Comment


Guideline
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Duplicate
Not in PICO
Not in PICO
Narrative review

Not in PICO


Narrative review


Narrative review


Not in PICO


Editorial


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Pre-1980


Not relevant; cancer patients not symptomatic patients


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

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Not in PICO

Not in PICO

Not in PICO

Not in PICO

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Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not relevant; cancer patients, not symptomatic primary care patients

Not in PICO
Not in PICO

Not relevant; cancer patients, not symptomatic primary care patients

**Review question:**

Which investigations of symptoms of suspected colorectal cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database Name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
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<td>Medline</td>
<td>1980-2013</td>
<td>1321</td>
<td>136</td>
<td>10/01/2013</td>
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<td>Premedline</td>
<td>1980-2013</td>
<td>35</td>
<td>4</td>
<td>14/01/2013</td>
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<td>Embase</td>
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<td>132</td>
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<td>Cochrane Library</td>
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<td>Psychinfo</td>
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<td>1</td>
<td>14/01/2012</td>
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<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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<td>21</td>
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<td>14/01/2013</td>
</tr>
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</table>

Total References retrieved (after de-duplication): 226

**Update Search**

<table>
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<tr>
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<td>2013-13/08/2014</td>
<td>118</td>
<td>1</td>
<td>13/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 25
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The studies were associated with a number of bias and validity issues. Two of the main issues to note relate to the patient selection methods employed and study settings, some of which were not clearly consecutive or random (and may therefore bias the results) or clearly transferable to UK-based primary care. Other issues of concern relate to missing data (and the concern that this may not be missing at random) and sub-optimal reference standards, which may both influence the results to an unknown extent.
### Study results

**Table 1: Colorectal cancer: Faecal occult blood**

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other results (95% CI)</th>
</tr>
</thead>
</table>
| Fijten (1995) | Faecal occult blood (Haemoccult) | 5/225      | 50%         | 82%         | Positive predictive value = 5%  
Negative predictive value = 99%  
False negativity rate = 50%  
95% CI cannot be calculated as 2-by2 table could not be extracted |
| Gillberg (2012) | Faecal occult blood (Haemoccult II) | 161/8928   | 75%         | 87%         | TP = 120  
FN = 41  
TN = 7585  
FP = 1182  
Positive predictive value = 9.2% (7.7-11)  
False negativity rate = 25%                                      |
| Jensen (1993) | Faecal occult blood              | 5/149      | 60%         | 79%         | TP = 3  
FN = 2  
TN = 114  
FP = 30                                              |
<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Other results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kok (2012)</td>
<td>Faecal occult blood (Clearview One Step immune-chemical)</td>
<td>19/386</td>
<td>84%</td>
<td>76%</td>
<td>Data only available for N = 376</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TP = 16 FN = 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 270 FP = 87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 15.5% (9.4-24.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 16%</td>
</tr>
<tr>
<td>Leicester (1984)</td>
<td>Faecal occult blood (Haemoccult)</td>
<td>4 cancers in 25 positive results out of 161 tests</td>
<td>56%</td>
<td>Not reported</td>
<td>Positive predictive value = 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI cannot be calculated as 2-by2 table could not be extracted</td>
</tr>
<tr>
<td>Stellon (1997)</td>
<td>Faecal occult blood (Haemoccult)</td>
<td>1/22</td>
<td>0%</td>
<td>76%</td>
<td>TP = 0 FN = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 16 FP = 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 0% (0-54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 100%</td>
</tr>
</tbody>
</table>

The data were not meta-analysed due to concerns about excessive heterogeneity (see forest plots below), differences in the tests employed and missing data. TP = true positives, FP = false positives, TN = true negatives, FN = false negatives. See forest plots below for the 95% CI for sensitivity and specificity.

Table 2: Colorectal cancer: Sigmoidoscopy

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Other results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaser (1989)</td>
<td>Rigid sigmoidoscopy</td>
<td>7/351</td>
<td>37.5% (10.2-74.1)</td>
<td>100% (98.6-100)</td>
<td>TP = 3 FN = 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 343 FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (31-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 62.5%</td>
</tr>
<tr>
<td>Jensen (1993)</td>
<td>Rectosigmoidoscopy</td>
<td>5/149</td>
<td>40% (7.3-83)</td>
<td>100% (96.8-100)</td>
<td>TP = 2 FN = 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 144 FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (19.8-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 60%</td>
</tr>
<tr>
<td>Kalra (1988)</td>
<td>Fibresigmoidoscopy</td>
<td>64 cancers in 216 abnormal findings in 541 patients</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Fibresigmoidoscopy unsuccessful in 31/541 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 4 cancers missed by fibresigmoidoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 29.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI cannot be calculated as 2-by2 table could not be extracted</td>
</tr>
<tr>
<td>Niv (1992)</td>
<td>Flexible sigmoidoscopy</td>
<td>5/255</td>
<td>Not reported</td>
<td>Not reported</td>
<td>TP = 4 FN = ≥ 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = ? FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (39.6-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = cannot be ascertained as negative cases did not</td>
</tr>
</tbody>
</table>
appear to be followed up

The data were not meta-analysed due to concerns about differences in the tests employed and missing data. TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Table 3: Colorectal cancer: Double-contrast barium enema

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen (1993)</td>
<td>Double-contrast barium enema</td>
<td>5/149</td>
<td>60%</td>
<td>100%</td>
<td>TP = 3 FN = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 144 FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (31-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 40%</td>
</tr>
<tr>
<td>Steine (1993)</td>
<td>Double-contrast barium enema</td>
<td>8/189</td>
<td>100%</td>
<td>98%</td>
<td>TP = 8 FN = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 177 FP = 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 66.7% (35.4-88.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 patient with anal cancer was not examined</td>
</tr>
<tr>
<td>Stellon (1997)</td>
<td>Double-contrast barium enema</td>
<td>2/22</td>
<td>50%</td>
<td>100%</td>
<td>TP = 1 FN = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = 20 FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (54.6-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = 50%</td>
</tr>
</tbody>
</table>

The data were not meta-analysed due to concerns about excessive heterogeneity (see forest plot below). TP = true positives, FP = false positives, TN = true negatives, FN = false negatives. See forest plots below for the 95% CI for sensitivity and specificity.

Forests plots
No evidence was found for colonoscopy, CT-colonoscopy/colonography, CT, and CEA.

Evidence statement(s):

Faecal occult blood (6 studies, N = 9871) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 0-84%, specificities that ranged from 76-87%, positive predictive values that ranged from 0-16%, and false negativity rates that ranged from 16-100% for colorectal cancer. All the studies were associated with 1-5 bias or applicability concerns (see also Table 1).

Sigmoidoscopy (5 studies, N = 1322) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 0-40%, specificities of up to 100%, positive predictive values that ranged from 0-100%, and false negativity rates that ranged from 60-100% for colorectal cancer. All the studies were associated with 0-5 bias or applicability concerns (see also Table 2).

Double-contrast barium enema (3 studies, N = 360) conducted in symptomatic patients presenting in a primary care setting is associated with sensitivities that ranged from 50-100%, specificities that ranged from 98-100%, positive predictive values that ranged from 66.7-100%, and false negativity rates that ranged from 0-50% for colorectal cancer. All the studies were associated with ≤ 2 bias or applicability concerns (see also Table 3).

Evidence tables

Fijten (1995)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: From September 1988 to April 1990, patients with rectal bleeding were recruited by 83 GPs in Limburg, with an average duration of participation of 11 months per doctor. Patients were included when overt rectal bleeding was the reason for encounter or when there was a history of recent (within the previous three months) rectal blood loss visible for the patient.</td>
</tr>
<tr>
<td>Exclusion criteria: Aged below 18 or above 75 years, pregnancy, urgent admission to hospital (for, e.g., a massive bleeding or acute abdominal pain), and if follow-up data were not available.</td>
</tr>
<tr>
<td><strong>Clinical setting:</strong> Primary care, Netherlands</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
</tr>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
</tr>
<tr>
<td>Gillberg (2012)</td>
</tr>
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<td><strong>PATIENT SELECTION</strong></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: All patients who between 2000-2005 had undergone faecal occult blood testing in one of the participating primary care centres.</td>
</tr>
<tr>
<td>Exclusion criteria: Repeat faecal occult blood testing for the same individual.</td>
</tr>
<tr>
<td>Clinical setting: Primary care, Sweden.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
</tr>
<tr>
<td>A. Risk of bias</td>
</tr>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
</tr>
<tr>
<td>A. Risk of bias</td>
</tr>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
</tr>
<tr>
<td>A. Risk of bias</td>
</tr>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

**NOTES**

Glaser (1989)

**PATIENT SELECTION**

A. risk of bias

Patient sampling | Retrospective patient series from a private family practice

Was a consecutive or random sample of patients enrolled? | Unclear

Was a case-control design avoided? | Yes

Did the study avoid inappropriate exclusions? | Unclear

Could the selection of patients have introduced bias? | Unclear risk

B. Concerns regarding applicability

Patient characteristics and setting | N = 351; 149 males, 202 females; mean age = 57.9 years.

Inclusion criteria: Patients who received a diagnostic sigmoidoscopy for a variety of clinical problems (e.g., rectal bleeding, abdominal pain or cramps, anaemia, change in bowel habits, hernia, constipation, proctalgia, weight loss, diarrhoea, pruritis ani, positive results of faecal occult blood test, rectal mass, palpable abdominal mass, condyloma, unusual flatulence, other) in which colorectal cancer or other significant disease was suspected in the author’s private family practice between 1977 and 1986.

Exclusion criteria: None listed.

Clinical setting: Canadian private family practice

Are there concerns that the included patients and setting do not match the review question? | High concern

**INDEX TEST**

A. Risk of bias

Index test | Rigid sigmoidoscopy

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes

Could the conduct or interpretation of the index test have introduced bias? | Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**REFERENCE STANDARD**

A. risk of bias

Reference standard(s) | Barium enema or colonoscopy

Is the reference standard likely to correctly classify the target condition? | Unclear

Were the reference standard results interpreted without knowledge of the results of the index tests? | No

Could the reference standard, its conduct, or its interpretation have introduced bias? | High risk
### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?  
**High concern**

### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td><strong>Unclear</strong></td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td><strong>High risk</strong></td>
</tr>
</tbody>
</table>

### NOTES

**Jensen (1993)**

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective? consecutive patient series from the Department of Radiology at Varberg Hospital, Sweden.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 149; 63 males, 86 females; mean age (range) = 64 (52-74) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>All patients referred with symptoms of colorectal disease by general practitioners to the Department of Radiology, Varberg Hospital, Sweden, for a double-contrast enema.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Swedish department of radiology.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td><strong>Unclear concern</strong></td>
</tr>
</tbody>
</table>

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Faecal occult blood on 3 separate samples using the Hemoccult II test (≥ 1 positive test indicate a positive result); 60-cm rectosigmoidoscopy; double-contrast barium enema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | **Low concern** |

### REFERENCE STANDARD

**A. risk of bias**
**Suspected Cancer: Appendix F (June 2015)**

### Reference standard(s)

<table>
<thead>
<tr>
<th><strong>Reference standard(s)</strong></th>
<th><strong>3-5 year follow up in the local cancer register.</strong></th>
</tr>
</thead>
</table>

| **Is the reference standard likely to correctly classify the target condition?** | **Unclear** |
| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | **No** |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | **Unclear risk** |

### B. Concerns regarding applicability

| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | **Low concern** |

### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th><strong>Flow and timing</strong></th>
<th><strong>All patients appear to be accounted for</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Were all patients included in the analysis? All test</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias? All tests</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### NOTES

- **Kalra (1988)**

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th><strong>Patient sampling</strong></th>
<th><strong>Retrospective consecutive patients who were referred for open access fibresigmoidoscopy in the UK.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th><strong>Patient characteristics and setting</strong></th>
<th><strong>N = 541; male:female ratio = 35:65. Abdominal pain was the commonest cause of open access referral followed by diarrhoea, rectal bleeding and constipation.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong> All patients referred for fibresigmoidoscopy for the first time during 1982-6. Open access referrals were defined as patients seen for the first time during the procedure and in whom no examination or investigations had previously been undertaken. <strong>Exclusion criteria:</strong> Hospital inpatients, patients attending the outpatient department for colorectal symptoms in whom results of other investigations were available. <strong>Clinical setting:</strong> UK open access fibresigmoidoscopy clinic.</td>
<td></td>
</tr>
<tr>
<td><strong>Are there concerns that the included patients and setting do not match the review question?</strong></td>
<td><strong>Unclear concern</strong></td>
</tr>
</tbody>
</table>

### INDEX TEST
### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Fibresigmoidoscopy (examination was deemed as a failure if in the absence of disease the rectosigmoid junction could not be negotiated).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up and some barium enema/colonoscopy studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the reference standard likely to correctly classify the target condition?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | High concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
</tr>
<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
</tr>
<tr>
<td><strong>Were all patients included in the analysis?</strong></td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
</tr>
</tbody>
</table>

### NOTES

- 2-by-2 cannot be extracted.

Kok (2012)

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Data from the CEDAR (Cost-effectiveness of a decision rule for abdominal complaints in primary care) study, an ongoing, prospective, cross-sectional, diagnostic study in 170 general practices in 2 regions (central and south) of Holland.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient | N = 8928 (3481 males/5447 females), age groups: 0-10: N = 100; 11-20: N = |
### Characteristics and Setting

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>619</td>
</tr>
<tr>
<td>31-40</td>
<td>820</td>
</tr>
<tr>
<td>41-50</td>
<td>1103</td>
</tr>
<tr>
<td>51-60</td>
<td>1458</td>
</tr>
<tr>
<td>61-70</td>
<td>1550</td>
</tr>
<tr>
<td>71-80</td>
<td>1876</td>
</tr>
<tr>
<td>81-90</td>
<td>1006</td>
</tr>
<tr>
<td>90+</td>
<td>92</td>
</tr>
</tbody>
</table>

Inclusion criteria:

Patients who between July 2009 – January 2011 consulted their GP for persistent (≥ 2 weeks) lower-abdomen complaints who also experienced ≥ 1 of the following: Rectal bleeding, altered defecation pattern, abdominal pain, fever, diarrhoea, weight loss, sudden onset in the elderly, or findings at physical examination suggestive or organic bowel disease (palpable abdominal or rectal mass).

Exclusion criteria:

Patients aged < 18 years, unable to give informed consent, previously diagnosed with organic bowel disease, or positive on triple faeces test (testing for intestinal parasites) not requiring endoscopy.

Clinical setting: Primary care, Holland.

### Are there concerns that the included patients and setting do not match the review question?

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

### Index Test

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index Test</th>
<th>Faecal occult blood test (Clearview One Step immunochemical point of care test).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or its interpretation differ from the review question? | Low concern |

### Reference Standard

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Colonoscopy (N = 351)/sigmoidoscopy (N = 21; other bowel examinations in N = 10) with biopsies if required according to routine clinical practice + 3 month follow-up for all patients with an inconclusive colonoscopy/sigmoidoscopy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

### Flow and Timing

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>Data only available for 376/386 included patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
</tbody>
</table>
Could the patient flow have introduced bias? | Unclear risk
--- | ---

Leicester (1984)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective random selection of consecutive? patients from UK general practice.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes probably</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was a case-control design avoided?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did the study avoid inappropriate exclusions?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the selection of patients have introduced bias?</th>
<th>Unclear risk</th>
</tr>
</thead>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 315; 121 males, 194 females; mean age (SD) = 58.2 (13.9) years, who were then randomly allocated to haemoccult testing or control. 161 patients (99.4%) in the haemoccult group complied with the testing and 24 tested positive.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Inclusion criteria:</th>
<th>Patients aged &gt; 40 years presenting in general practice with any abdominal or bowel complaints.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria:</th>
<th>None listed.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Clinical setting:</th>
<th>UK GP</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Haemoccult testing</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Patients with a negative haemoccult test were managed conventionally by their GP including specialist referral, if appropriate. Patients with a positive haemoccult test underwent flexible sigmoidoscopy and double-contrast barium enema at the earliest opportunity, followed by urgent outpatient appointment and colonoscopy where indicated.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>No</th>
</tr>
</thead>
</table>

| Could the reference standard, its conduct, or its interpretation have introduced bias? | High risk |
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>High concern</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>No</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

<table>
<thead>
<tr>
<th>Published as abstract only. 2-by-2 table cannot be extracted</th>
</tr>
</thead>
</table>

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective consecutive patient series from an open-access flexible sigmoidoscopy outpatient clinic in Israel.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### Patient characteristics and setting

- N = 255; 123 males, 132 females; mean age (range) = 54 (10-90) years. The patients were referred with the following indications: Change in bowel habit (N = 103), rectal bleeding (N = 107), abdominal pain (N = 45), anaemia (3%), weight loss (N = 15), Fx colon cancer (N = 26), positive faecal occult blood test (N = 26), “post polyp.” (N = 11).

- **Inclusion criteria:** All patients referred for open-access flexible sigmoidoscopy by general practitioners.
- **Exclusion criteria:** Bad state of health, referral error.
- **Clinical setting:** Israeli open-access flexible sigmoidoscopy outpatient clinic.

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Flexible sigmoidoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. risk of bias

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>When a polyp or cancer was found, the patient was referred for total colonoscopy. Negative results did not appear to be followed up.</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>No</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Flow and timing</th>
<th>As the negative results did not appear to be followed up, the false negative rate cannot be ascertained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Could the patient flow have introduced bias? All tests</td>
<td>High risk</td>
<td></td>
</tr>
</tbody>
</table>

**NOTES**

Steine (1993)

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Retrospective randomly selected patient series from the Central Roentgen Institute in Oslo, Norway.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 190; age range = 45-79 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Random sample (9%) of patients referred by GPs for double-contrast barium enema at the Central Roentgen Institute.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients not aged 45-79.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Norwegian roentgen institute.</td>
<td></td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? Unclear concern

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th>Double-contrast barium enema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### Reference Standard

<table>
<thead>
<tr>
<th>A. Risk of Bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Colonoscopy (with histology)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

### Flow and Timing

<table>
<thead>
<tr>
<th>A. Risk of Bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias? All tests</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Notes

One patient with anal cancer was not examined

---

Stellon (1997)

### Patient Selection

<table>
<thead>
<tr>
<th>A. Risk of Bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective? consecutive patient series from semi-rural UK general practice with a patient list between 2400-3400 during the study period.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Patient characteristics and setting: N = 26; 5 males, 21 females; age range = 51-87 years.

**Inclusion criteria:** All patients aged > 50 years found to have iron deficiency anaemia (< 12 g/dl haemoglobin and/or mean corpuscular volume < 80 fl with ferritin ≤ 16 ng/l) between January 1989 and March 1994.

**Exclusion criteria:** None listed.

**Clinical setting:** UK GP

**Are there concerns that the included patients and setting have?** Low concern
<table>
<thead>
<tr>
<th>do not match the review question?</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDEX TEST</td>
</tr>
<tr>
<td>A. Risk of bias</td>
</tr>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
</tr>
<tr>
<td>A. Risk of bias</td>
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<tr>
<td>Reference standard(s)</td>
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<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
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<tr>
<td>A. Risk of bias</td>
</tr>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis? FOB</td>
</tr>
<tr>
<td>Were all patients included in the analysis? BE</td>
</tr>
<tr>
<td>Were all patients included in the analysis? FS</td>
</tr>
<tr>
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</tr>
<tr>
<td>Could the patient flow have introduced bias? BE</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias? FS</td>
</tr>
<tr>
<td>NOTES</td>
</tr>
</tbody>
</table>

**References**

Included studies


Excluded studies (with excl reason)


Not in PICO


Guideline


Not in PICO


Not in PICO

(2014) If you want to avoid colonoscopy, you still have effective options. Colonoscopy is best for early colorectal cancer prevention, but stool testing also works pretty well if you have it every year. Harvard men's health watch, 18: 4-5.

Narrative review

(2014) - If you want to avoid colonoscopy, you still have effective options. Colonoscopy is best for early colorectal cancer prevention, but stool testing also works pretty well if you have it every year. - Harvard Mens Health Watch, 18: 4-5.

Duplicate
Not in PICO

Same as Halligan 2013

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Present no data in PICO

Not in PICO

Not in PICO


Borhan-Manesh, F. (2009) "Low caliber stool" and "pencil thin stool" are not signs of colo-rectal cancer. [Review] [30 refs]. *Digestive Diseases & Sciences*, 54: 208-211.


Not in PICO (referred patients)

Not in PICO

Published as abstract only. Not enough information can be extracted to ascertain final relevance, but it appears to be not in PICO

Not in PICO

Not in PICO

Not in PICO

Mixed symptomatic/asymptomatic population; cannot extract the information for symptomatic patients only; large number did not receive reference standard

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review
Not in PICO (only 17.5% primary care patients)

Duplicate

Not in PICO

Not in PICO

Narrative review/guideline

Not in PICO

Not in PICO

Published as abstract only. Not enough information can be extracted to ascertain final relevance, but it appears to be not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO
Not in PICO
Protocol
Not in PICO (referred population)
Narrative review
Same as Halligan 2013
Narrative review
Test not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
126: 95-107.
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
SR, but no meta-analysis. The relevant included studies will be assessed separately.
Not in PICO
Not in PICO (think referred population)
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

N = 6 (and these 6 likely to be referred patients)

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO (secondary care, emailed author and confirmed with Willie)


Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


In Russian. Not enough relevant information can be extracted to determine relevance, but on the basis of what can be extracted, it is unlikely to be in PICO.
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO


In Serbian, N = 300 that I think are all referred patients, i.e., Not in PICO

Not in PICO

Not in PICO

Not available from the British library. Have emailed author for the paper, but not received a response so far.

Not in PICO

Not in PICO

Same as Bekkink

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Review of guidelines

Not in PICO
Not in PICO (not diagnostic test accuracy study)

Not in PICO

Guideline

Comment

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Duplicate, same as MacMillan 1984
Narrative review

Guideline

Not in PICO

Unavailable from British Library, in Japanese, and don't think in PICO

Not in PICO

Not in PICO

Not in PICO (not a diagnostic test accuracy study)

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Systematic review: Any relevant data will be reported per study

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Outcome not in PICO. Referred population?

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO (screening)

Not in PICO

Guideline
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO (think referred population)
Narrative review
Not in PICO
In Chinese, but thinks it’s referred patients, so not in PICO
Not in PICO
Comment
Narrative review
Narrative review
Not in PICO


ANAL CANCER

Review question:
What is the risk of anal cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

<table>
<thead>
<tr>
<th>Database name</th>
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<td>1</td>
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<td>All-2012</td>
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<tr>
<td>Cochrane Library</td>
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<td>132</td>
<td>2</td>
<td>12/09/2012</td>
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<td>Psychinfo</td>
<td>All-2012</td>
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<td>12/09/2012</td>
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<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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<td>11</td>
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<tr>
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<td>0</td>
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<td></td>
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Update Search

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<th>No of references retrieved</th>
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<td>26/08/2014</td>
</tr>
<tr>
<td>Premedline</td>
<td>9/2012-26/08/2014</td>
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<td>26/08/2014</td>
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<tr>
<td>Embase</td>
<td>9/2012-26/08/2014</td>
<td>61</td>
<td>1</td>
<td>26/08/2014</td>
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<tr>
<td>Cochrane Library</td>
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<td><strong>1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study results

No evidence was found.

Included studies

None

Excluded studies (with excl reason)

- The Dutch College of General Practitioners guideline for rectal bleeding. [Dutch]. Huisarts en Wetenschap 52[1], 23-38. 2009.
  Excl reason: Guideline

  Excl reason: Not in PICO

  Excl reason: Not in PICO

  Excl reason: Not in PICO

  Excl reason: Not in PICO

References
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Billingham, R. P. Anorectal miscellany: pilonidal disease, anal cancer, Bowen's and Paget's diseases, foreign bodies, and hidradenitis suppurativa. [Review] [29 refs]. Primary Care; Clinics in Office Practice 26[1], 171-177. 1999.
Excl reason: Narrative review

Excl reason: Pre-1980

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO
da Costa e Silva, Gimenez, F. S., Guimaraes, R. A., Camelo, R. T., Melo, M. N., de Barros, F. S.,
Daumas, A., Cabral, C. R., and Guimaraes, E. L. Anal cytology as a screening method for early
detection of anal cancer: are hydrophilic cotton smears really unsatisfactory?. [Portuguese]. Acta
cirurgica brasileira / Sociedade Brasileira para Desenvolvimento Pesquisa em Cirurgia 20[1], 109-
Excl reason: Not in PICO
Dahl, O. and Fluge, O. Anal cancer. [Norwegian]. Tidsskrift for Den Norske Laegeforening 128[2], 198-
Excl reason: Narrative review
Damin, D. C., Rosito, M. A., Gus, P., Spiro, B. L., Amaral, B. B., Meurer, L., Cartel, A., and
Schwartsmann, G. Sentinel lymph node procedure in patients with epidermoid carcinoma of the
Excl reason: Not in PICO
Excl reason: Narrative review
deSouza, N. M., Hall, A. S., Puni, R., Gilderdale, D. J., Young, I. R., and Kmiot, W. A. High resolution
magnetic resonance imaging of the anal sphincter using a dedicated endoanal coil. Comparison
of magnetic resonance imaging with surgical findings. Diseases of the Colon & Rectum 39[8],
926-934. 1996.
Excl reason: Not in PICO
Devaraj, B. and Cosman, B. C. Expectant management of anal squamous dysplasia in patients with
HIV. Diseases of the Colon & Rectum 49[1], 36-40. 2006.
Excl reason: Not in PICO
Di, Comite A. and De, Vita L. [Congenital telangiectasic (pyogenic) granuloma of the anus: a rare
Excl reason: Narrative review
12-4-1968.
Excl reason: Not in PICO
Dietz, C. A. and Nyberg, C. R. Genital, oral, and anal human papillomavirus infection in men who
have sex with men. [Review]. Journal of the American Osteopathic Association 111[3:Suppl 2],
Excl reason: Not in PICO
Dindo, D., Nocito, A., Schettle, M., Clavien, P. A., and Hahnloser, D. What should we do about anal
condyloma and anal intraepithelial neoplasia? Results of a survey. Colorectal Disease 13[7], 796-
801. 2011.
Excl reason: Not in PICO
American Family Physician 85[6], 624-630. 2012.
Excl reason: Narrative review
Ferrandiz-Pulido, C. [Early detection of anal intraepithelial neoplasia in high-risk patients]. [Spanish].
Actas Dermo-Sifiliograficas 102[10], 754-756. 2011.
Excl reason: Narrative review
Ferron, P., Young, S., Doyle, F., Symes, S., Powell, A., Diaz-Mendez, N., and Rosa-Cunha, I. A case
illustration about the importance of integrating women's anal health in an HIV primary care
Excl reason: Not in PICO
Ficari, F., Fazi, M., Garcea, A., Nesi, G., and Tonelli, F. Anal carcinoma occurring in Crohn's disease
patients with chronic anal fistula. I supplementi di Tumori : official journal of Societa italiana di
cancerologia. et[3], S31-Jun. 11-11-1111.
Excl reason: Not in PICO

Excl reason: Not in PICO (surgical specimens)


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Narrative review


Excl reason: Narrative review


Excl reason: Not in PICO


Excl reason: Not in PICO

Greene, M. D. Diagnosis and management of HPV-related anal dysplasia. [Review] [65 refs]. Nurse Practitioner 34[5], 45-51. 2009.

Excl reason: Narrative review


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Narrative review


Excl reason: Narrative review
Excl reason: Not in PICO

Excl reason: Not in PICO

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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Kratzer, G. L. What the family physician should know about proctology. GP 38[5], 126-132. 1968.
Excl reason: Pre-1980

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO (secondary care setting)

Excl reason: Not in PICO

Lindsey, K., Decristofaro, C., and James, J. Anal pap smears: Should we be doing them? Journal of the American Academy of Nurse Practitioners 21[8], 437-443. 2009.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Mlakar, B. Proctoscopy should be mandatory in men that have sex with men with external anogenital warts. Acta Dermatovenerologica Alpina, Pannonica et Adriatica 18[1], 7-11. 2009.
Excl reason: Not in PICO

Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Ong, J., Jit-Fong, L., Ming-Hian, K., Boon-Swee, O., Kok-Sun, H., and Eu, K. W. Perianal mucinous adenocarcinoma arising from chronic anorectal fistulae: a review from a single institution. Techniques in Coloproctology 11[1], 34-38. 2007.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Prieto, Reyes M. and Vazquez, Marquez L. [Anal epidermoid carcinoma: a rare incidence or a rare diagnosis?]. [Review] [53 refs] [Spanish]. Revista Espanola de Enfermedades Digestivas 89[2],


Diseases of the Colon and Rectum 54[4], 433-441. 2011.
Excl reason: Not in PICO (screening)

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

**Review question:**

Which investigations of symptoms of suspected anal cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references</th>
<th>No of references</th>
<th>Finish date of</th>
</tr>
</thead>
</table>

Suspected Cancer: Appendix F (June 2015) Page 667 of 1735
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The only included study was associated with a number of bias and validity issues, with the main concerns...
relating to whether the results are representative of those of UK-based primary care practice and the fact that negative sigmoidoscopy results were not verified or followed up.

### Study results

**Table 1: Anal cancer: Sigmoidoscopy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Other results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niv (1992)</td>
<td>Flexible sigmoidoscopy</td>
<td>5/255</td>
<td>Not reported</td>
<td>Not reported</td>
<td>TP = 4 FN = ≥ 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TN = ? FP = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive predictive value = 100% (39.6-100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False negativity rate = cannot be ascertained as negative cases did not appear to be followed up</td>
</tr>
</tbody>
</table>

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

No evidence was found for proctoscopy.

**Evidence statement(s):**

Sigmoidoscopy (1 study, N = 255) conducted in symptomatic patients presenting in a primary care setting is associated with a positive predictive values of 100%. The included study was associated with 3 bias/applicability concerns (see also Table 1).

**Evidence tables**

**Niv (1992)**

<table>
<thead>
<tr>
<th><strong>PATIENT SELECTION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td><strong>Patient sampling</strong></td>
</tr>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
</tr>
</tbody>
</table>
**Did the study avoid inappropriate exclusions?** Yes

**Could the selection of patients have introduced bias?** Low risk

### B. Concerns regarding applicability

| Patient characteristics and setting | N = 255; 123 males, 132 females; mean age (range) = 54 (10-90) years. The patients were referred with the following indications: Change in bowel habit (N = 103), rectal bleeding (N = 107), abdominal pain (N = 45), anaemia (3%), weight loss (N = 15), Fx colon cancer (N = 26), positive faecal occult blood test (N = 26), “post polyp.” (N = 11). |

**Inclusion criteria:** All patients referred for open-access flexible sigmoidoscopy by general practitioners.

**Exclusion criteria:** Bad state of health, referral error.

**Clinical setting:** Israeli open-access flexible sigmoidoscopy outpatient clinic.

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

| **Index test** | Flexible sigmoidoscopy |

**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes

**Could the conduct or interpretation of the index test have introduced bias?** Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or its interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

#### A. Risk of bias

| **Reference standard(s)** | When a polyp or cancer was found, the patient was referred for total colonoscopy. Negative results did not appear to be followed up. |

**Is the reference standard likely to correctly classify the target condition?** No

**Were the reference standard results interpreted without knowledge of the results of the index tests?** No

**Could the reference standard, its conduct, or its interpretation have introduced bias?** High risk

#### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

### FLOW AND TIMING

#### A. Risk of bias

| **Flow and timing** | As the negative results did not appear to be followed up, the false negative rate cannot be ascertained |

**Was there an appropriate interval between index test and reference standard?** Unclear

**Did all patients receive the same reference standard?** No

**Were all patients included in the analysis?** No

**Could the patient flow have introduced bias? All tests** High risk
References

Included studies

Excluded studies (with excl reason)
Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

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Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Narrative review

Narrative review


**BREAST CANCER**

**Review question:**
What is the risk of breast cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
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<td>122</td>
<td>22/04/2013</td>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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Total References retrieved (after de-duplication): 284

**Update Search**

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<th>No of references found</th>
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</thead>
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<tr>
<td>Cochrane Library</td>
<td>4/2013-12/08/2014</td>
<td>138</td>
<td>0</td>
<td>12/08/2014</td>
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<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>4/2013-12/08/2014</td>
<td>95</td>
<td>2</td>
<td>12/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 30
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note is that 3/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP and a fourth study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Two of the studies also employed reference standards that are subject to an unclear risk of bias, one study only reported episode-(not patient)based analyses, which seems to result in overestimation of the PPVs, and one study had a large amount of missing data; all of which must be born in mind when evaluating the evidence contributed by these studies.
### Study results

Table 1: Breast cancer: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prevalence</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast pain</td>
<td>Women aged 40-79 years</td>
<td>1.8 (0.6-4.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4/221 episodes in 372 women</td>
</tr>
<tr>
<td>Eberl (2008)</td>
<td>Breast pain</td>
<td>Women aged &lt;25 – 75+ years</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11/1191</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Breast pain</td>
<td>Women aged 25- &gt;80 years</td>
<td>5.9 (1-21.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/34</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast pain</td>
<td>Women aged 40-49 years</td>
<td>0.17 (0.16-0.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 50-59 years</td>
<td>0.8 (0.52-1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 60-69 years</td>
<td>1.2 (0.73-2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 70+ years</td>
<td>2.8 (1.4-5.4)</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast mass</td>
<td>Women aged 40-79 years</td>
<td>10.7 (6.9-16.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21/196 episodes in 372 women</td>
</tr>
<tr>
<td>Eberl (2008)</td>
<td>Breast lump/mass</td>
<td>Women aged &lt;25 – 75+ years</td>
<td>8.1 (6.3-10.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60/741</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 40-49 years</td>
<td>4.8 (3.6-5.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 50-59 years</td>
<td>8.5 (6.7-11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 60-69 years</td>
<td>25 (17-36)</td>
</tr>
<tr>
<td>Author</td>
<td>Condition</td>
<td>Age Group</td>
<td>Cases</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------</td>
<td>----------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Breast lump</td>
<td>Women aged 70+ years</td>
<td>48 (35-61)</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump</td>
<td>Women aged 25-&lt;80</td>
<td>10 (3.7-22.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>5/50</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump &lt; 2 cm</td>
<td>Women aged 25-&lt;80</td>
<td>7.7 (0.4-37.9)</td>
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<tr>
<td></td>
<td></td>
<td>years</td>
<td>1/13</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump ≥ 2 cm</td>
<td>Women aged 25-&lt;80</td>
<td>14.3 (2.5-43.8)</td>
</tr>
<tr>
<td></td>
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<td>years</td>
<td>2/14</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Round, oblong mass</td>
<td>Women aged 25-&lt;80</td>
<td>25 (4.5-64.4)</td>
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<tr>
<td></td>
<td></td>
<td>years</td>
<td>2/8</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Irregular in shape</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/3</td>
</tr>
<tr>
<td></td>
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<td>years</td>
<td>2/16</td>
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<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Tethered to skin or chest wall</td>
<td>Women aged 25-&lt;80</td>
<td>40 (7.3-83)</td>
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<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Smooth texture</td>
<td>Women aged 25-&lt;80</td>
<td>18.2 (3.2-52.2)</td>
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<td></td>
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<td>years</td>
<td>2/11</td>
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<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Irregular texture</td>
<td>Women aged 25-&lt;80</td>
<td>33.3 (6-75.9)</td>
</tr>
<tr>
<td></td>
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<td>years</td>
<td>2/6</td>
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<tr>
<td>McCowan (2011)</td>
<td>Discrete breast lump: Spongy texture</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-94.5)</td>
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<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/1</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple discharge</td>
<td>Women aged 40-49</td>
<td>1.2 (NR)</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple discharge</td>
<td>Women aged 50-59</td>
<td>2.1 (0.81-5.1)</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple discharge</td>
<td>Women aged 60-69</td>
<td>2.3 (NR)</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple discharge</td>
<td>Women aged 70+ years</td>
<td>23 (NR)</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Nipple discharge</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-37.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/9</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Nipple discharge: Bloodstained</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-53.7)</td>
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<td></td>
<td></td>
<td>years</td>
<td>0/5</td>
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<tr>
<td>McCowan (2011)</td>
<td>Nipple discharge: Persistent</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-43.9)</td>
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<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/7</td>
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<tr>
<td>Barton (1999)</td>
<td>Skin or nipple change</td>
<td>Women aged 40-79</td>
<td>3 (0.5-11.3)</td>
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<tr>
<td><em>Episode-based analysis</em></td>
<td>2/67 episodes in 372 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eberl (2008)</td>
<td>Nipple complaint</td>
<td>Women aged &lt;25 – 75+ years</td>
<td>1.9 (0.6-5.1)</td>
</tr>
<tr>
<td></td>
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<td>years</td>
<td>4/210</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Nipple eczema</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-94.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/1</td>
</tr>
<tr>
<td>McCowan (2011)</td>
<td>Nipple retraction</td>
<td>Women aged 25-&lt;80</td>
<td>0 (0-53.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>0/5</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple retraction</td>
<td>Women aged 40-49</td>
<td>NR (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years</td>
<td>4 cases, 0 controls</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple retraction</td>
<td>Women aged 50-59</td>
<td>2.6 (NR)</td>
</tr>
<tr>
<td>Walker (2014)</td>
<td>Nipple retraction</td>
<td>Women aged 60-69</td>
<td>3.4 (NR)</td>
</tr>
</tbody>
</table>
Walker (2014) & Nipple retraction & Women aged 70+ years & 12 (NR) \\
Barton (1999) & Breast lumpiness & Women aged 40-79 years & 2.6 (0.1-15.4) \\
  *Episode-based analysis* & & 1/38 *episodes in 372 women* \\
McCowan (2011) & Breast thickening & Women aged 25- >80 years & 11.1 (0.6-49.3) \\
  & & 1/9 \\
McCowan (2011) & Breast abscess & Women aged 25- >80 years & 0 (0-94.3) \\
  & & 0/1 \\
Barton (1999) & Other breast symptom & Women aged 40-79 years & 0 (0-43.9) \\
  *Episode-based analysis* & & 0/7 *episodes in 372 women* \\
Eberl (2008) & Other breast complaint & Women aged <25 – 75+ years & 1.7 (0.7-3.8) \\
  & & 6/361 \\
McCowan (2011) & Other breast symptom (skin nodules, general nodularity) & Women aged 25- >80 years & 25 (1.3-78.1) \\
  & & 1/4 \\
McCowan (2011) & Lymphadenopathy & Women aged 25- >80 years & 40 (7.3-83) \\
  & & 2/5 \\
Oudega (2006) & Deep vein thrombosis & All patients & 0.93 (0.3-2.53) \\
  & & 4/430 \\

CI = Confidence interval. Please note the calculations of the positive predictive values differ between the studies with Barton (1999), Eberl (2008), McCowan (2011) and Oudega (2006) using (TP)/(TP+FP) and Walker (2014) using Bayesian statistics due to the case-control design of this study. No meta-analyses were performed as there were not enough studies for this analysis to be performed with both Barton (1999) and Walker (2014) being ineligible for inclusion due to the episode-based analysis and case-control design, respectively.

### Table 2: Breast cancer: Symptom combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)%</th>
</tr>
</thead>
</table>
| Barton (1999) *Episode-based analysis* | Breast pain (reported twice in an episode??) | Women aged 40-79 years | 1.2 (0.2-4.7)* \\
  | & & 2/169 *episodes in 372 women* | 
| Barton (1999) *Episode-based analysis* | Breast mass (reported twice in an episode??) | Women aged 40-79 years | 10.7 (6.5-16.8)* \\
  | & & 17/159 *episodes in 372 women* | 
| Barton (1999) *Episode-based analysis* | Skin or nipple change (reported twice in an episode??) | Women aged 40-79 years | 2 (0.1-11.8)* \\
  | & & 1/51 *episodes in 372 women* | 
| Barton (1999) *Episode-based analysis* | Breast lumpiness (reported twice in an episode??) | Women aged 40-79 years | 4 (0.2-22.3)* \\
  | & & 1/25 *episodes in 372 women* | 
| Barton (1999) *Episode-based analysis* | Breast pain and breast mass | Women aged 40-79 years | 6.5 (1.1-22.8) \\
  | & & 2/31 *episodes in 372 women* | 
| Walker (2014) | Breast lump and breast pain | Women aged 40-49 years | 4.9 (NR) 
| Walker (2014) | Breast lump and breast pain | Women aged 50-59 years | 5.7 (NR) 
| Walker (2014) | Breast lump and breast | Women aged 60-69 | 6.5 (NR) 

Suspected Cancer: Appendix F (June 2015)
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Symptom(s)</th>
<th>Patient Group</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker (2014)</td>
<td>Breast lump and breast pain</td>
<td>Women aged 70+ years</td>
<td>&gt; 5 (NR)</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast pain and skin or nipple change</td>
<td>Women aged 40-79 years</td>
<td>0 (0-26.8) 0/14 episodes in 372 women</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast pain and breast lumpiness</td>
<td>Women aged 40-79 years</td>
<td>0 (0-43.9) 0/7 episodes in 372 women</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast mass and skin or nipple change</td>
<td>Women aged 40-79 years</td>
<td>100 (5.5-100) 1/1 episodes in 372 women</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Breast mass and breast lumpiness</td>
<td>Women aged 40-79 years</td>
<td>20 (10.5-70.1) 1/5 episodes in 372 women</td>
</tr>
<tr>
<td>Barton (1999)</td>
<td>Skin or nipple change and breast lumpiness</td>
<td>Women aged 40-79 years</td>
<td>0 (0-94.5) 0/1 episodes in 372 women</td>
</tr>
</tbody>
</table>

CI = Confidence interval. Please note the calculations of the positive predictive values differ between the studies with Barton (1999) using (TP)/(TP+FP) and Walker (2014) using Bayesian statistics due to the case-control design of this study. * These results are presented in a table (Table 5) entitled “Breast Cancer Diagnosis According to Combinations of Symptoms”, it is however unclear what they reflect: Since they are similar, but not identical to those presented as single symptoms, they cannot be that; also, since only 56 women had 2 episodes and 35 women had 3 or more episodes, these results cannot represent a repeat presentation of the same symptom across episodes; which leaves repeat presentations of these symptoms within episodes as an option. However, that is not clearly reported either in the paper, so it cannot be confirmed what exactly these results reflect.

Evidence statement(s):

The positive predictive values for breast cancer of single symptoms presenting in a primary care setting ranged from 0% (for an 'irregularly shaped discrete breast lump', a 'breast lump with a spongy texture', nipple discharge, nipple eczema, nipple retraction, breast abscess, 'other breast symptom') to 48% (for breast lump in women aged 70+ years; 5 studies, N = 24269), but these extreme PPVs were based on small patient/episode numbers. The studies were subject to 1-2 bias or applicability concerns (see also Table 1).

The positive predictive values for breast cancer of symptom pairs presenting in a primary care setting ranged from 0% (for breast lumpiness with 'skin or nipple change' or breast pain, and for breast pain with 'skin or nipple change') to 100% (for breast mass and 'skin or nipple change'; 2 studies, N = 21239), but these extreme PPVs were based on small patient/episode numbers. The studies were subject to 1-2 bias/applicability concerns (see also Table 2).

Evidence tables

Barton (1999)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
</tbody>
</table>
Was a consecutive or random sample of patients enrolled? Yes  
Was a case-control design avoided? Yes  
Did the study avoid inappropriate exclusions? Yes (probably)  
Could the selection of patients have introduced bias? Low risk  

### B. Concerns regarding applicability

| Patient characteristics and setting | 372 women presented with breast symptoms in 539 separate episodes; although most women had only 1 breast-symptom episode, 56 women presented twice and 35 women presented three or more times. Total number of episodes = 539, consisting of 221 for pain, 196 for mass, 67 for skin or nipple change, 38 for lumpiness, 7 for other, and 69 episodes where no specific symptom was documented. 23/372 women had breast cancer. 24/539 episodes lead to a diagnosis of breast cancer. |

**Inclusion criteria:** “Female HMO members with automated medical records .... were eligible. We selected a cohort of 2400 women who were continuously enrolled in the HMO from 1 July 1983 through 30 June 1995. Women 40 to 69 years of age as of 1 July 1983 were sampled in a random, age-stratified manner to include 1200 women in the age group 40 to 49, 600 women in the age group 50 to 59 years, and 600 women in the age group 60 to 69 years.” “Information on all breast-related encounters between 1 July 1983 and 30 June 1993 was collected from a computerized medical record”. “The reason for each visit was determined to be screening (unrelated to any previously recognized breast abnormality or symptom) or diagnostic (to investigate an abnormality noted by the patient, by the clinician at an earlier examination or on previous mammography). This study reports on diagnostic visits related to patient symptoms.”  
**Exclusion criteria:** Women with insurance coverage in addition to that of the HMO during the study period (N = 1), had breast cancer before 1 July 1983 (N = 4), or had reduction mammoplasty or prophylactic mastectomy before or during the study period (N = 11).  
Clinical setting: Health maintenance organisation, USA.

**Are there concerns that the included patients and setting do not match the review question?** Unclear concern

**INDEX TEST**

**A. Risk of bias**

| Index test | Patient symptoms were classified as follows:  
1) Mass (a single lump or nodule)  
2) Pain (a report of pain or tenderness in either breast or bilaterally)  
3) Skin or nipple change (including nipple discharge)  
4) Multiple lumps or nodules (often described by patients as “lumpiness” and by clinicians as “fibrocystic” or “diffuse cystic change”)  
5) Other symptoms (such as increasing size of breast)  
Physical examination findings were recorded by using the same five categories. More than one symptom/finding could be documented.  
“We defined a breast-symptom episode as the initial patient visit and all subsequent related visits and evaluations; a woman could have more than one episode during the 10-year study. We defined a new episode as beginning with a breast-symptom visit more than 6 months after the end of any previous episode. We considered a breast-symptom visit within 6
months of a previous episode to be the beginning of a new episode when the symptom was in the contralateral breast.”

<table>
<thead>
<tr>
<th>Question</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>“Breast cancer outcomes were determined for all women from 1 July 1983 to 30 June 1994 to ensure adequate time for follow-up of all breast-symptom episodes. To determine outcomes, we reviewed the computerized medical records and the HMO’s tumor registry for diagnoses of breast cancer.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>It appears that all patients are accounted for, but the results reported are not patient-based, but rather episode-based.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

The episode-based analysis undertaken in this paper makes the results less comparable with other results presented for this guideline than would otherwise have been the case, and the net result of this type of analysis may be an underestimation of the PPVs.

It is unclear whether the patients included span the ages of 40-69 years or 40-79 years, as reported in the inclusion criteria and discussion, and in Table 1, respectively.
### Eberl (2008)

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the Transition Project database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 2503 females, aged from below 25 to above 65 years who had the following breast-related symptoms: Breast lump/mass (N = 741), breast pain (N = 1191), nipple complaint (N = 210), and other breast complaint (N = 361). 81/2503 patients had breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients with breast-related encounters in the Transition Project “Between 1985 and 2003, the Transition Project in the Netherlands comprehensively and prospectively coded office visits to family physicians based on the International Classification of Primary Care (ICPC). The term encounter is synonymous with an office visit in the United States. For the Transition Project, 58 Dutch family physicians routinely coded data on reasons for encounter, diagnoses, and interventions for all episodes of care they provided between 1985 and 2003. Given that each patient in the Netherlands must register with a family practice office, clinic-based participation is reflective of the broader population-based health care system. Only visits to physicians participating in the Dutch Transition project are contained in the study database; visits to nurse-practitioners and physician’s assistants were not included.”</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None reported.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Dutch primary care.</td>
</tr>
</tbody>
</table>

#### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>“Breast symptoms include specific complaints, such as breast lump/mass, breast pain or tenderness, and nipple discharge; however, it is clear that women also come to physicians with fear of breast cancer and anxiety regarding their family history and risk of cancer. Fear of breast cancer is considered a unique reason for encounter in the Transition Project.”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

**A. risk of bias**

| Reference standard(s) | “A final diagnosis of benign (absence of neoplasm) vs malignant (including ductal carcinoma in situ, lobular carcinoma in situ, and histologic atypical)” |
disease was assigned to each breast-related reason for encounter,”
“Participating family physicians completed all coding for their patients; no cancer registry match was performed.”

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for in the results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Although it does not explicitly stated that women with pre-existing breast cancer were excluded, even if they consulted with a breast-related episode, it appears that they were.

**McCowan (2011)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from 11 UK-based general practices.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>97 women, aged: 25-39 years: N = 28; 40-49 years: N = 31; 50-59 years: N = 14; 60-69 years: N = 11; 70-79 years: N = 10; ≥ 80 years: N = 3; Past history: Any breast problems: N = 60; previous clinic attendance: N = 43; breast cancer: N = 3; breast lump: N = 37; breast abscess: N = 9; breast pain: N = 41.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>“11 participating general practices in the region agreed to recruit all women who attended for an initial consultation regarding symptomatic breast problems between January 2006 and June 2007.”</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>“Patients were excluded if the consultation was related to issues around cosmetic surgery or breastfeeding problems.”</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Primary care, UK</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
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</tbody>
</table>
## INDEX TEST

### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Symptomatic breast problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

## REFERENCE STANDARD

### A. Risk of bias

**Reference standard(s)**

> “All patients in the two cohorts were traced for a diagnosis of breast cancer using the regional prospective cancer audit in the year following their initial consultation. This audit identifies all diagnosed breast cancers to allow reporting on the standards of care against national targets and is the basis of cancer registry returns.”

| **Is the reference standard likely to correctly classify the target condition?** | Yes |
| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

### B. Concerns regarding applicability

| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

## FLOW AND TIMING

### A. Risk of bias

**Flow and timing**

All patients appears to be accounted for, but only 97/202 eligible patients took part (mainly due to lack of telephone contact details being available/correct; 16/118 contacted patients declined participation and 5/118 contact patients failed to return the written consent).

| **Was there an appropriate interval between index test and reference standard?** | Yes |
| **Did all patients receive the same reference standard?** | Yes |
| **Were all patients included in the analysis?** | No |
| **Could the patient flow have introduced bias?** | High risk (missing data as per above) |

## NOTES

Oudega (2006)

## PATIENT SELECTION

### A. Risk of bias

**Patient sampling**

Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in Holland.

<p>| <strong>Was a consecutive or random sample of patients enrolled?</strong> | Yes |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, Holland.</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

**INDEX TEST**

| A. Risk of bias | Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis. |
|.Cookies|  |
| Index test |  |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

**REFERENCE STANDARD**

| A. Risk of bias | Reference standard(s) 2 years follow up. |
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

| A. Risk of bias | Flow and timing All patients appear to be accounted for |
| Was there an appropriate interval between index test and reference standard? | Yes |
### Did all patients receive the same reference standard?
Yes

### Were all patients included in the analysis?
Yes

### Could the patient flow have introduced bias?
Low risk

### NOTES
In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

---

**Walk**er (2014)

**PATIENT SELECTION**

**A. risk of bias**

**Patient sampling**
- Matched case-control study using patients in the UK’s Clinical Practice Research Database (CPRD).

**Was a consecutive or random sample of patients enrolled?**
- No

**Was a case-control design avoided?**
- No

**Did the study avoid inappropriate exclusions?**
- Yes

**For diagnostic case-control studies:**
- Attempts were made within the design or analysis to balance the comparison groups for potential confounders?
  - Yes

**For diagnostic case-control studies:**
- The groups were comparable at baseline, including all major confounding and prognostic factors?
  - Yes

**Could the selection of patients have introduced bias?**
- High risk

**B. Concerns regarding applicability**

**Patient characteristics and setting**

**Cases:**
- 3994 women, median age at diagnosis = 63 (IQR = 55-74) years; median number of consultations: in the year before index = 9 (IQR = 5-15), in 6 months before index = 9 (IQR = 4-16); UK.

**Controls:**
- 16873 women; median number of consultations: in the year before index = 7 (IQR = 4-13), in 6 months before index = 6 (IQR = 2-12); UK.

**Inclusion criteria:**
- Cases: Women aged ≥ 40 years with one of 56 identified breast tumour diagnostic codes in the CPRD between 1 January 2000 and 31 December 2009, with min. 1 year of data before diagnosis. The first instance of a breast cancer code was assigned the data of diagnosis/index date.
- Controls: 5 randomly selected controls matched on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.

**Exclusion criteria:**
- Males diagnosed with breast cancer, ill-defined medcodes giving multiple sites of cancer; skin cancer of the breast; cases with a mastectomy, chemotherapy or radiotherapy medcode > 90 days before the index date (as this strongly suggested that the index date was wrong); controls diagnosed with breast cancer (or having a mastectomy) before the index date; and women with no consultations in the year before diagnosis.

**Clinical setting:** UK primary care

**Are there concerns that the included patients and setting do not match the review question?**
- Low concern

---

**INDEX TEST**
### A. Risk of bias

**Index test**

All symptoms, signs or abnormal investigations previously recorded in the breast cancer literature and cancer charity websites were studied. “The CPRD stores clinical information in just over 100,000 medcodes, each describing a facet of primary care, such as a symptom. There are several codes for each symptom, differing usually in a qualifier such as duration or severity, so generally containing more information than a specific Read code. All the codes pertaining to individual symptoms were collated into single symptom libraries.” “Occurrences of symptoms in the year before the index date were identified. Features were only retained in the study if they occurred in ≥1% of the cases or controls (this was invariably cases). We assembled a list of plausible laboratory abnormalities *a priori* using the literature and our clinical knowledge (WH, CH). We also identified all abnormal laboratory results in the year before the index date, using the local laboratory’s normal range, which is supplied with the data. We considered women without a test to be equivalent to those with a normal result. Some abnormal tests were grouped: abnormal liver function was defined as the presence of any liver enzyme above the normal range. The variable ‘raised inflammatory markers’ was defined as a raised erythrocyte sedimentation rate, C-reactive protein or plasma viscosity. These simplifications were necessary as different localities in the UK contributing to the CPRD have different tests available.”

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Low concern

### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>One of 56 identified breast tumour diagnostic codes in the CPRD.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

### FLOW AND TIMING

**A. risk of bias**

Flow and timing

A total of 26162 women were identified, 21755 controls and 4407 cases. Of the controls the following exclusions were applied: Mastectomy medcode before index date of case (N = 564), breast cancer before the index date of
the case (N = 380), no GP consultations in the year before the index date of the case (N = 2238), and controls of excluded cases (N = 1700). Of the cases the following exclusions were applied: Males (N = 51), ill-defined codes giving multiple sites of cancer (N = 52), skin cancers in breast (N = 18), cancers in sites other than breast (N = 2), medcodes > 3 months pre-index of mastectomy (N = 150) or chemotherapy./radiotherapy (N = 45), no GP consultations in the year before the index date of case (N = 89), and no controls (N = 6).

Was there an appropriate interval between index test and reference standard?  Yes

Did all patients receive the same reference standard?  Yes

Were all patients included in the analysis?  Yes

Could the patient flow have introduced bias?  Low risk

NOTES
23 symptoms and 22 abnormal test results were considered initially. The proportion of patients with a recorded fracture did not differ between cases (1.8%) and controls (1.6%).

References

Included studies

Excluded studies (with excl reason)
Not in PICO
Narrative review
Not in PICO
Not in PICO
Abdolmohammadi, A., Sears, W., Rai, S., Pan, J., Alexander, J. & Kloecker, G. (2014) - Survey of primary care physicians on therapeutic approaches to lung and breast cancers. - *Southern*


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


In Slovak. Don't think it is in PICO (cytologic examinations of the nipple secretions of N = 904)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


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Not in PICO

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Not in PICO

Not in PICO

Not in PICO (does not go into detail about symptoms, only report "comon cancer related symptoms by cancer", 275/379 reported symptoms already investigated, not broken down by investigation/symptom and cancer status

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO (breast cancer cases cannot be linked to specific symptoms)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Narrative review
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Not in PICO


Cochrane Database of Systematic Reviews.
Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Systematic review without meta-analysis. Included studies checked for relevance.

Not in PICO

Not in PICO

Narrative review

Not in PICO

Abstract only, not enough information to ascertain relevance.

From National Breast Cancer Centre Sydney Australia SR. Not in PICO

From National Breast Cancer Centre Sydney Australia SR. Not in PICO
Not in PICO

Narrative review

Outcomes not in PICO. Presented data only for cancer as a whole, not by individual cancers.

Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Duplicate

Not in PICO

Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO

7. Not in PICO
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Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Symptoms not linked with cancers; analysis based on number of codes, not patients.

Symptoms not linked with cancers; analysis based on number of codes, not patients.

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

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Not in PICO

Not in PICO
Narrative review

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Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO, I think. Setting seems to be surgery department

Not in PICO


From Hider HTA. Systematic review without meta-analysis. Checked for relevant studies.


Niishiguchi, T., Hishimoto, T., Funahashi, S., Takatsuka, Y. & Kawahara, T. (1992) [Clinical usefulness of carcinoembryonic antigen measurement in nipple discharge as an adjunctive tool for diagnosis...
Not in PICO

Not in PICO

Not in PICO

Not in PICO

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Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Narrative review

Narrative review

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Narrative review


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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO (secondary care)
Not in PICO
Not in PICO
From Hider HTA. Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Guideline

Guideline

Not in PICO

Systematic review. Checked for relevant studies (which have been included separately).

Narrative review
From National Breast Cancer Centre Sydney Australia SR. Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO (secondary care)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Review question:

Which investigations of symptoms of suspected breast cancer should be done with clinical responsibility retained by primary care?

Results

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
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<td>1509</td>
<td>290</td>
<td>25/04/2013</td>
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<td>14</td>
<td>25/04/2013</td>
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</table>

Total References retrieved (after de-duplication): 553

<table>
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Total References retrieved (after de-duplication): 36
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The study was associated with a number of bias and validity issues. The following issues compromise the validity and applicability of this study, (1) only about half of the patient population were patients relevant to the current question, to the extent that Dutch primary care is comparable to UK-based primary care, and no subgroup analyses were presented for this group of patients, (2) the results of the ultrasound scan was interpreted non-blinded to the results of the mammography and clinical examination, which biases the accuracy of the outcome measures study, most likely upwards, and (3) the time span between the index test and reference standard is unclear and the results are therefore compromised to an unknown extent.

Study results
Table 1: Breast cancer: Study results

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI) %</th>
<th>Specificity (95% CI) %</th>
<th>Other results (95% CI)</th>
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<tr>
<td>Flobbe (2003)</td>
<td>Mammography</td>
<td>129/3835 breasts, 127/2020 patients</td>
<td>82.9 (75.1-88.8)</td>
<td>91.9 (90.9-92.7)</td>
<td>TP = 107 FN = 22, TN = 3405 FP = 301, Positive predictive value = 26.2 (22.1-30.8)%, Negative predictive value = 99.4 (99.5-99.7)%, False negativity rate = 17.1%</td>
</tr>
<tr>
<td>Flobbe (2003)</td>
<td>Ultrasound</td>
<td>129/3835 breasts, 127/2020 patients</td>
<td>87.6 (80.4-92.5)%</td>
<td>95.5 (94.8-96.1)%</td>
<td>TP = 113 FN = 16, TN = 3556 FP = 167 These values from the paper are wrong as the total of negatives should be 3706 and not 3723 as is the case here. This means that apart from the sensitivity and false negativity rate, the remaining results for ultrasound should be interpreted with extreme caution. Positive predictive value = 40.4 (34.6-46.4)% Negative predictive value = 99.6 (99.3-99.7)% False negativity rate = 12.4%</td>
</tr>
</tbody>
</table>

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

No evidence was found for FNA.

Evidence statements:

Mammography (1 study, N = 2020 patients/3835 breasts) is associated with a sensitivity of 82.9%, a specificity of 91.9%, a positive predictive value of 26.2%, and a false negativity rate of 17.1% for breast cancer. Ultrasound (1 study, N = 2020 patients/3835 breasts) is associated with a sensitivity of 87.6%, a specificity of 95.5%, a positive predictive value of 40.4%, and a false negativity rate of 12.4% for breast cancer. The study was associated with 4 bias or applicability concerns (see also Table 1).

Evidence tables

Flobbe (2003)

<table>
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<tr>
<td>A. risk of bias</td>
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<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
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<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

Patient characteristics and setting

N = 2020 (20 males/2000 females), mean (range) age = 50.2 (16.8-90.3) years; Referred by: GP (N = 1044), surgeons (N = 712), other specialists (N = 264); Indications for referral: Palpable breast lump (N = 470), other breast symptoms, such as pain or skin or nipple abnormalities (N = 486), follow up of prior breast malignancy(N = 438), follow up of prior benign breast disease (N = 152), mammography abnormalities detected at screening (N = 144), family history of breast cancer (N = 234), patient anxiety (N = 13), other asymptomatic reasons (N = 83).

The results are only reported for breasts as the unit of analysis, not patients: There were 3835 breasts examined in 2020 patients, with 129 malignancies found in 127 patients (2 bilateral breast cancers).

Inclusion criteria: “Between October 1, 1999, and August 1, 2000, all consecutive patients referred to our radiology department for diagnostic breast imaging underwent additional US after a CE [clinical examination] and MAM [mammography]”.

Exclusion criteria: When ultrasound could not be performed because of logistic reasons or when no informed consent was given.

Clinical setting: Unclear, the Netherlands

Are there concerns that the included patients and setting do not match the review question? High concern

INDEX TEST

A. Risk of bias

Index test

Bilateral clinical performed while the patient was in standing and sitting positions, followed by mammography (standard craniocaudal and mediolateral oblique examination; Siemens Mammomat-2 unit/Kodak Min-R film screen combination) followed by whole-breast ultrasound (model ATL5000, 12.5-MHz linear array transducer; Philips Medical Systems, Best, the Netherlands) both scored on a scale from 1-5 with increasing suggestion of malignancy (1 and 2 defined as negative results and 3-5 defined as positive results). All examinations were performed and interpreted with full knowledge of prior test results.

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Unclear risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern

REFERENCE STANDARD

A. Risk of bias

Reference standard(s)

Pathologic results of core needle biopsy, excision biopsy and other surgical interventions during a follow up of 12 months. An additional 2 months were added, accounting for administrative routing of test results at the end of the follow up period. Pathologic results were retrieved from the hospital pathology department and the Dutch Network and National Database for Pathology, to which all Dutch hospital pathology departments are linked. Breast cancer status was considered negative when non pathologic condition was reported in either system.
Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing

Of the 2720 scheduled imaging examinations, 112 were cancelled and 84 were excluded from the study due to earlier inclusion. 279 did not receive the additional ultrasound for logistical reasons, and 255 refused consent. The patients excluded from the study had a comparable prevalence of breast cancer, age distribution, reason for referral, and imaging interpretation.

Was there an appropriate interval between index test and reference standard? Unclear

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Unclear risk

NOTES

References

Included studies


Excluded studies (with excl reason)

Not in PICO

Not in PICO

Not in PICO

Duplicate of Hider (1999)

Not in PICO

Not in PICO


Narrative review


Not in PICO

(2010) [Third revision of the National Consensus on Diagnosis and Treatment of Breast Cancer (first of three parts)]. [Spanish]. Ginecologia y Obstetricia de Mexico, 78: 72-82.

Consensus guideline


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO (screening)


Not in PICO


Guideline


Guideline


Duplicate


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO (secondary care)


In Russian, not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Not in PICO


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Abstract only. Not enough information can be extracted to ascertain relevance, but I think it is not in PICO.


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Narrative review


Narrative review


Narrative review


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Narrative review

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Narrative review

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Not in PICO (screening)

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Narrative review

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N = 3014, of whom 1931 received mammography only, 996 received mammography + US, and 87
received US only, but results only reported for them all irrespective of which test they received, thus results cannot be split by test.

Narrative review


Not in PICO


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Narrative review/Not in PICO

Not in PICO

Not in PICO (only 377/1376 received reference standard)

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

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Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO (only US or mammography-positive patients received reference standard, so not possible to establish the number of true negatives and false negatives)

Not in PICO

Not in PICO

Outcomes not in PICO and cannot be calculated from the presented data. Setting is unclear

Narrative review/Not in PICO

Not in PICO (S&S: "The Center for the diagnosis of breast disease in Maribor", so think secondary care, and no symptoms linked to breast cancer; test: no relevant outcomes)

Not in PICO

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Not in PICO


Narrative review


Narrative review


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Hasert, V. (1990) [Diagnostic imaging of the breast--a survey]. [Review] [57 refs] [German]. *Radiologia Diagnostica, 31*: 425-432.

Narrative review


Narrative review


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Abstract only, not enough information to ascertain relevance.


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Not in PICO


Narrative review


Not in PICO


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Outcomes not in PICO. Presented data only for cancer as a whole, not by individual cancers.


Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up


Narrative review


Narrative review


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Patient Navigation Program. Health Promotion Practice, 14: 105-112.
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Narrative review


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Narrative review

18: 661-665.
Duplicate of Nishizawa (1983)
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Narrative review

[Ultrasound examination of the breast with 7.5 MHz and 13 MHz-transducers: scope for 
improving diagnostic accuracy in complementary breast diagnostics?]. [German]. Ultrasschall in 
der Medizin, 26: 209-215.
Not in PICO

Narrative review

recognition of breast cancer in Germany. Abridged version for medical practitioners. [German]. 
Guideline

scanning in the follow-up of breast cancer patients. A study of 1000 cases. Journal of Cancer 
Research & Clinical Oncology, 116: 486-491.
Not in PICO

Radiologia Medica, 86: 687-694.
Not in PICO

Not in PICO

imaging: a primer for the primary care physician. [Review] [60 refs]. Journal of the American 
Board of Family Practice, 18: 478-490.
Not in PICO

Not in PICO

cancer (review). [Review] [33 refs]. Oncology Reports, 8: 153-156.
Narrative review

Comparative analysis of early diagnostic tools for breast cancer. [Chinese]. Chinese Journal of 
Oncology, 34: 877-880.
Not in PICO

Tubular carcinoma of the breast: mammographic and sonographic features. AJR American Journal 
of Roentgenology, 174: 253-257.
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Narrative review

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Narrative review

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Narrative review

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Narrative review

Not in PICO (secondary care)

Not in PICO

In Chinese. Not enough information can be extracted to ascertain relevance, but I think it is not in PICO

Not in PICO

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Narrative review

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Narrative review


Not in PICO (screening)


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Narrative review/Not in PICO
ENDOMETRIAL CANCER

Review question:
What is the risk of endometrial cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

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Total References retrieved (after de-duplication): 144

Update Search

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Total References retrieved (after de-duplication): 14
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included studies in the figure below. The main issues to note are that one of the studies was conducted in a Dutch primary care setting, which may limit the applicability of the result to UK primary care and this study may also not have accounted for all the patients. Moreover, another study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors of the study may have gone some way in counteracting this influence. Finally, the population in one of the studies comprises a mix of ‘old’ and ‘new’ investigated or uninvestigated symptoms, and it is unclear how directly applicable this sample is to the current question.
## Study results

### Table 1: Endometrial cancer: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain (first presentation to GP)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.1)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain (repeated symptom)</td>
<td>Women ≥ 55 years</td>
<td>0.2 (0.1-0.1) As reported, but CI is not correct</td>
</tr>
<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.04 (0.002-0.25) 1/2585</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Haematuria (first presentation to GP)</td>
<td>Women ≥ 55 years</td>
<td>0.7 (0.5-1)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Vaginal discharge (first presentation to GP)</td>
<td>Women ≥ 55 years</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>Parker (2007)</td>
<td>Post-menopausal bleeding</td>
<td>All women</td>
<td>1.7 (1.4-2) 170/10122</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding (first presentation to GP)</td>
<td>Women ≥ 55 years</td>
<td>4 (3.2-5.2)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding (repeated symptom)</td>
<td>Women ≥ 55 years</td>
<td>9.6 (6.2-17.8)</td>
</tr>
<tr>
<td>Droogendijk</td>
<td>Anaemia</td>
<td>All women</td>
<td>0.63 (0.03-4.01) 1/158</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Low haemoglobin (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.1)</td>
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<tr>
<td>Walker (2013)</td>
<td>High platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.1)</td>
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<tr>
<td>Walker (2013)</td>
<td>High glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.2)</td>
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</tbody>
</table>

Walker (2013) calculated the positive predictive values using Bayesian statistics.

### Table 2: Endometrial cancer: Symptom combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
</table>
Walker (2013) calculated the positive predictive values using Bayesian statistics. NR = not reported.

**Evidence statement(s):**

For uterine cancer the positive predictive values of single symptoms (4 studies, N = 25134) presenting in primary care ranged from 0% (for post-menopausal bleeding in women aged 40-44

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom Description</th>
<th>Population</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding + vaginal discharge</td>
<td>Women ≥ 55 years</td>
<td>8.3 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding + abdominal pain</td>
<td>Women ≥ 55 years</td>
<td>2.9 (1.6-5.7)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding + high platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>5.4 (3.1-10.2)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Post-menopausal bleeding + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>3.4 (1.3-9.5)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain + haematuria</td>
<td>Women ≥ 55 years</td>
<td>0.7 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain + vaginal discharge</td>
<td>Women ≥ 55 years</td>
<td>0.5 (0.2-1.3)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain + low haemoglobin (test)</td>
<td>Women ≥ 55 years</td>
<td>0.2 (0.1-0.4)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain + high platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Abdominal pain + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Vaginal discharge + haematuria</td>
<td>Women ≥ 55 years</td>
<td>2.2 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Vaginal discharge + low haemoglobin (test)</td>
<td>Women ≥ 55 years</td>
<td>0.6 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Vaginal discharge + high platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>1.4 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Vaginal discharge + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>0.6 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Haematuria + low haemoglobin (test)</td>
<td>Women ≥ 55 years</td>
<td>2.7 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Haematuria + high platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>1.9 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Haematuria + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>1.1 (NR)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Low haemoglobin (test) + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>0.2 (0.1-0.2)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>Low haemoglobin (test) + high platelets (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Walker (2013)</td>
<td>High platelets (test) + high glucose (test)</td>
<td>Women ≥ 55 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
</tbody>
</table>
years) to 9.6% (for repeated post-menopausal bleeding). The included studies were associated with 0-2 bias/applicability concerns (see also Table 1).

For uterine cancer the positive predictive values of symptom combinations (1 study, N = 12269) presenting in primary care ranged from 0.1% (for high platelets in combination with either abdominal pain, low haemoglobin or high glucose) to 9.1% (for post-menopausal bleeding combined with haematuria). The included study was associated with 1 bias concern (see also Table 2).

**Evidence tables**

Droogendijk (2011)

<table>
<thead>
<tr>
<th><strong>PATIENT SELECTION</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Retrospective peripheral hospital laboratory database study serving 265 GPs in Dordrecht (Holland).</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>N = 287; 129 men, 158 women; median (range) age = 70 (19-87) years. Inclusion criteria: All women aged &gt; 50 years and all men aged ≥ 18 years who between January 2004 and December 2005 were diagnosed with iron-deficiency anaemia (haemoglobin &lt; 13.7 g/dl in men and &lt; 12.1 g/dl in women, and a serum ferritin level &lt; 25 µg/l for men and &lt; 20 µg/l for women). Exclusion criteria: Patients with a known history of iron-deficiency anaemia in the previous 2 years, a history of gastrointestinal malignancy or congenital haemoglobinopathy. Clinical setting: GPs in Holland</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INDEX TEST</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Risk of bias</strong></td>
</tr>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>It is unclear if all patients are accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

In addition to the 24 patients with colorectal cancer, 3 patients had gastric cancer, 1 patient had oesophageal cancer and 1 patient had locally invasive endometrial cancer.

---

**Hallissey (1990)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective consecutive patient series from a group of 10 general practices in England.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 2585 aged &gt; 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Primary care, England.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
</tbody>
</table>

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Dyspepsia of any degree</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Upper gastrointestinal endoscopy within 4 weeks and follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>2659 patients were seen and 2585 attended for investigation</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).</td>
</tr>
<tr>
<td><strong>PARKER (2007)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series using patients in the QResearch database.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>Rectal bleeding: N = 29007 (13931, males, 15076 females); median age (inter-quartile range) = 54 (40-69) years. Post-menopausal bleeding: N = 10122 (10122 females); median age (inter-quartile range) = 58 (54-67) years.</td>
</tr>
</tbody>
</table>
**Inclusion criteria:**
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system before 1 April 1998 and had complete data up to 1 April 2005. Patients were included if they were registered with an eligible practice at any time between 1 April 1998 and 31 March 2003, had been registered with the practice for ≥ 12 months and had a first-ever consultation for rectal bleeding and were aged ≥ 25 years, or post-menopausal bleeding and were aged ≥ 40 years, between 1 April 1998 and 31 March 2003.

**Exclusion criteria:** Previous record of colorectal cancer (for patients presenting with rectal bleeding) and endometrial cancer (for patients presenting with post-menopausal bleeding).

**Clinical setting:** Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>First ever presentation of rectal bleeding, first ever presentation of post-menopausal bleeding.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Could the conduct or interpretation of the index test have introduced bias?**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up (relevant cancer for rectal bleeding was colorectal cancer; relevant cancer for post-menopausal bleeding was endometrial cancer).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were all patients included in the analysis?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the patient flow have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

- Attempts were made within the design or analysis to balance the comparison groups for potential confounders?
  - Yes

- The groups were comparable at baseline, including all major confounding and prognostic factors?
  - Yes

**Could the selection of patients have introduced bias?**

- High risk

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases: N = 2732; median number of consultations in the year before the index date = 14 (IQR = 9-21); median number of consultations in the 6 months before the index date = 9 (IQR = 6-14); median age at diagnosis = 67 (IQR = 59-75); UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls: N = 9537; median number of consultations in the year before the index date = 8 (IQR = 4-14); median number of consultations in the 6 months before the index date = 4 (IQR = 2-8); UK.</td>
</tr>
<tr>
<td>Inclusion criteria: Cases: A list of 30 uterine tumour diagnostic codes was collated from the GPRD master code library, all mapping to Read Codes within the B43..00 tree for uterine cancer. Codes relating to cervical cancer were omitted. All women aged ≥40 years with one of these codes, diagnosed between 1 January 2000 and 31 December 2009, were identified. The date of the first cancer code in the records was taken to be the date of diagnosis; this was labelled the index date. Controls: For each case, five controls, matched to the case by year of birth, sex, and practice, were randomly selected, using a computer-generated sequence. The matched controls were assigned the index date of their case. Exclusion criteria: The following exclusion criteria were applied: Cases with &lt;1 year of data meeting GPRD quality standards before the first diagnostic code; leiomyosarcoma (the GPRD had ascribed all leiomyosarcomas to uterine origin: as there are several possible sites for leiomyosarcomas, all were excluded); diagnosis before 1 January 2000; controls diagnosed with uterine cancer before the index date; metastatic cancer from a non-uterine primary cancer; women with a recorded hysterectomy before the index date; and women with no consultations in the year before the index date. Women with a hysterectomy recorded &gt;3 months before their first uterine cancer</td>
<td></td>
</tr>
</tbody>
</table>
Code were also excluded, as the date of diagnosis was unreliable; if the discrepancy was <3 months, the index date was taken to be the date of the hysterectomy.

Clinical setting: Primary care UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

All symptoms, signs or abnormal investigations previously recorded in the uterine cancer literature and cancer charity websites were studied. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥2% of cases or controls. A list of plausible laboratory abnormalities was assembled a priori, using the literature and the authors’ clinical knowledge. All abnormal laboratory results in the year before the index date were also identified, using the local laboratory’s normal range, which is supplied with the data. Women without a test were considered to be equivalent to those with a normal result. Some abnormal tests were grouped: abnormal liver function was defined as the presence of any liver enzyme above the normal range. The variable ‘raised inflammatory markers’ was defined as a raised erythrocyte sedimentation rate, C-reactive protein, or plasma viscosity. These simplifications were necessary, as different localities in the UK contributing to the GPRD have different tests available.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>
| *For diagnostic case-control studies:*  
Investigators were kept ‘blind’ to other important confounding and prognostic factors? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

**Reference standard(s)**

Uterine cancer code in the UK’s General Practice Research Database.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined | Low concern |
### Flow and Timing

A total of 18841 patients were identified, 15675 controls and 3166 cases. Of the controls the following exclusions were applied: Uterine cancer before index date of case (N = 41), hysterectomy before index date of case (N = 2732), case excluded (N = 2074) and no data in year pre-index date (N = 1291). Of the cases the following exclusions were applied: No controls (N = 13), sarcoma (N = 251), metastatic cancer (N = 3), and hysterectomy recorded > 3 months prior to cancer index date (N = 167).

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Notes

One subgroup analysis examined women aged ≥55 years, as a proxy for being postmenopausal, and for this analysis all abnormal menstrual bleeding variables were categorised as postmenopausal bleeding.

### References

**Included studies**


**Excluded studies (with reason)**


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO (secondary care)


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO (secondary care)


Narrative review


Narrative review


Narrative review


Narrative review

Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO as not reported separately for primary care, if indeed any studies are where primary care retains the clinical responsibility


Not in PICO as not reported separately for primary care, if indeed any studies are where primary care retains the clinical responsibility


Not in PICO
Narrative review

In German. It is "Not in PICO" for signs nad symptoms and I also think it is secondary care, so "Not in PICO" for tests.

Not in PICO

Not in PICO

Not in PICO (secondary care)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Hou, D. M., Xie, Y. & He, W. (2009) Early diagnosis of endometrial disorder in women with postmenopausal bleeding by three-dimensional transvaginal sonography and hysterosonography. [Chinese]. *Zhonghua yi xue za zhi*, 89: 4. In Chinese, not enough information can be extracted to ascertain eligibility status, but I think it is "Not in PICO"


Narrative review


Not in PICO


Not in PICO


Not in PICO


Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Narrative review/guideline


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Duplicate


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review

Suspected Cancer: Appendix F (June 2015)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Ronghe, R. & Gaudoin, M. (2010) Women with recurrent postmenopausal bleeding should be re-investigated but are not more likely to have endometrial cancer. Menopause International, 16: March.

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Narrative review


Systematic review, relevant papers added separately


Not in PICO


Not in PICO (secondary/tertiary care)


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


In Polish. I don’t think it is in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO (secondary care)
Not in PICO

Not in PICO

**Review question:**
Which investigations of symptoms of suspected endometrial cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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Total References retrieved (after de-duplication): 181

**Update Search**

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<td>0</td>
<td>13/08/2014</td>
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</tbody>
</table>

Total References retrieved (after de-duplication): 6
Study results

No evidence was identified pertaining to the diagnostic accuracy of transvaginal/abdominal ultrasound, pipelle sampling, CA125 or hysteroscopy in patients with suspected endometrial cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)

Guideline

Not in PICO

In German. Not enough information can be extracted, but I think it is secondary care and not in PICO

Duplicate
455-458. 
Duplicate
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
In Turkish, not enough information can be extracted, but I think it is secondary care and "not in PICO"
Not in PICO
Narrative review
Not in PICO (secondary care)
In German. Not enough information can be extracted, but I think it is secondary care and not in PICO
Not in PICO (secondary care)
Narrative review
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

In Rumanian. I think it is secondary care, so not in PICO

Narrative review
Not in PICO as not reported separately for primary care, if indeed any studies are where primary care reatins the clinical responsibility

Not in PICO as not reported separately for primary care, if indeed any studies are where primary care reatins the clinical responsibility

Not in PICO

Not in PICO as not reported separately for primary care, if indeed any studies are where primary care reatins the clinical responsibility

Not in PICO as not reported separately for primary care, if indeed any studies are primary care

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

In Italian. I think it is secondary care, so not in PICO

Not in PICO (secondary care)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

analysis (DARE structured abstract). Cancer, 89: 1765-1772.
Not in PICO as not reported separately for primary care, if indeed any studies are where primary care retains the clinical responsibility
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO (secondary care)
Not in PICO
Not in PICO

Not in PICO


Narrative review


Not in PICO


Not in PICO


Think it's not in PICO for endometrial as cancer prevalence = 14%, and not reported separately for primary care, if indeed any studies are primary care


Not in PICO


Narrative review


Narrative review


Not in PICO (secondary care)


In Bulgarian. Not enough information can be extracted, but I think it is "Not in PICO"

In Bulgarian, not enough information can be extracted to ascertain eligibility status, but I think it is "Not in PICO"

Jaffe, J. S. Use of outpatient endometrial biopsy in a population with intellectual disability.

Ref Type: Generic
Ref ID: 87
Reprint: Not in File
Abstract: Background: To demonstrate the feasibility of outpatient endometrial sampling to evaluate abnormal uterine bleeding in a population of women with intellectual disability.
Method: Retrospective chart review was completed of all endometrial biopsies performed on women attending a dedicated gynaecology clinic for women with intellectual disability over an 8-year period. A fine calibre disposable suction curette was utilized. Results: Of the 64 women sampled, adequate tissue for pathological diagnosis was obtained in 84%. Of the 35 with post-menopausal bleeding, a pathological diagnosis was reported in 86% including one endometrial adenocarcinoma. Intravenous sedation was necessary in 12 cases. Conclusions: Endometrial sampling can be successfully performed on an outpatient basis in women with intellectual disability. Most were performed without sedation in a clinic setting suggesting that this technique is generally applicable in this population. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract)
Notes: DB - PsycINFO
AN - Peer Reviewed Journal: 2008-01714-011
MA - Jaffe, Joshua S.: jjaffe@snet.net
Narrative review
Narrative review
Not in PICO (133/169 included women were asymptomatic)
Not in PICO
Not in PICO
Abstract only, not enough information can be extracted to ascertain relevance, but I think it is not in PICO

Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO (asymptomatic women)


Not in PICO


In Bulgarian, not enough information can be extracted to ascertain eligibility status, but I think it is a narrative review


Narrative review/guideline


Narrative review


Not in PICO (secondary care, confirmed by Willie)


Narrative review


Not in PICO

Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review

Not in PICO (secondary care)

Narrative review

Not in PICO

Narrative review

In Russian. Not enough information can be extracted, but I think it is "Not in PICO"

Narrative review

Guideline

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Okeahialam, M. G., Jones, S. E. & O'Donovan, P. J. (2001) Outcome of outpatient micro-hysteroscopy performed for abnormal bleeding while on hormone replacement therapy. *Journal of Obstetrics..."
& Gynaecology, 21: 277-279.
Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
401-404.
Not in PICO (secondary care)

Narrative review
management of asymptomatic postmenopausal patients with suspicious ultrasound findings of
the uterine endometrium - Correlation with sonographic and histologic findings. [German].
Geburtshilfe und Frauenheilkunde, 59: 163-166.
Not in PICO
Schneider, A. (2011) Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage
endometrial cancer: A prospective multicentre study (SENTI-ENDO). [German]. Onkologie, 17:
725-726.
Not in PICO
48: 1597-1598.
Not in PICO
Not in PICO
Not in PICO
General Practice, 47: 387-391.
Narrative review
Shun-Jiao, Z. (1990) Value of multiple punch biopsy plus endocervical curettage in early diagnosis of
cancer of the cervix uteri. [Chinese]. Chinese Journal of Clinical Oncology, 17: 3-5.
Not in PICO
Narrative review
value to detect endometrial pathology in postmenopausal symptomatic women without
hormone replacement therapy. Archives of Gynecology and Obstetrics, 282: S118.
Not in PICO
thickness should prompt biopsy in postmenopausal women without vaginal bleeding. Ultrasound
in Obstetrics and Gynecology, 24: 558-565.
Not in PICO
Not in PICO
hysteroscopy in the diagnostic of perimenopausal metrorrhagia. A study of 35 cases].
[Romanian]. Revista Medico-Chirurgicala a Socetatii de Medici Si Naturalisti Din Iasi, 109: 813-
816.
Not in PICO
Not in PICO
In Italian, limited information provided about patients, but I believe it is "Not in PICO"

Not in PICO

Not in PICO

Not in PICO

Not in PICO (secondary care)

Narrative review

Not in PICO

Not in PICO

Not in PICO (87.9% women were asymptomatic)

Not in PICO

Guideline

Narrative review

Not in PICO
Not in PICO
Not in PICO (secondary care)
Not in PICO
Not in PICO
Not in PICO
Not in PICO
CERVICAL CANCER

Review question:
What is the risk of cervical cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

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Total References retrieved (after de-duplication): 96

Update Search

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</table>

Total References retrieved (after de-duplication): 18
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issues to note are that the study results are compromised by both the non-consecutive/non-random patient selection as well as by the under-specification of the symptom under investigation and the setting, which may not be directly applicable to UK-based primary care.

Study results
Table 1: Cervical cancer: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muris (1995)</td>
<td>Non-acute abdominal complaints</td>
<td>All women</td>
<td>0.5 (0.1-1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3/598: 1 cervix, 2 other cancer of the female genital</td>
</tr>
</tbody>
</table>
Evidence statement(s):

Non-acute abdominal complaints presenting in primary care do not appear to be associated with an increased risk of cervical cancer (PPV = 0.5%; 1 study, N = 598). The included study was associated with 3 bias/applicability concerns (see also Table 1).

Evidence tables

Muris (1995)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem.</td>
</tr>
<tr>
<td>Exclusion criteria: None listed.</td>
</tr>
<tr>
<td>Clinical setting: GPs in Holland</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
</tbody>
</table>

INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
</tr>
</tbody>
</table>

REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
</tbody>
</table>
Could the reference standard, its conduct, or its interpretation have introduced bias?  Low risk

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?  Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing  All patients appear to be accounted for

Was there an appropriate interval between index test and reference standard?  Unclear

Did all patients receive the same reference standard?  Yes

Were all patients included in the analysis?  Yes

Could the patient flow have introduced bias?  Low risk

NOTES  Other cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), kidney (1/933), colorectal (4/933), and other and unspecified sites (2/933).

References

Included studies

Excluded studies (with reason)
   Not in PICO
   Narrative review
   Not in PICO
   Not in PICO
   Not in PICO
   Not in PICO
   Narrative review

Narrative review


Not in PICO


Narrative review


Ordered for endometrial tests


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO
Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review


Hertel, H. & Hillemanns, P. (1111) Pre-menopausal vaginal bleeding in cases of gynaecological malignancy. [German]. *Gynakologische Endokrinologie*, 5: May.


Narrative review

Narrative review

Not in PICO

Not in PICO (secondary care)

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO (secondary care, confirmed by Willie)

Not in PICO

Not in PICO

Duplicate

Not in PICO

Suspected Cancer: Appendix F (June 2015)


Not in PICO

Not in PICO

Not in PICO

Not in PICO (not symptomatic patients presenting to the GP)

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Meeting abstract, does not appear to be in PICO

Guideline

Narrative review
Narrative review

Not in PICO

Not in PICO

Not in PICO (included under endometrial cancer)

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

**Review question:**
Which investigations of symptoms of suspected cervix cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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<tr>
<td>Premedline</td>
<td>1980-2013</td>
<td>158</td>
<td>6</td>
<td>10/06/2013</td>
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<tr>
<td>Embase</td>
<td>1980-2013</td>
<td>2221</td>
<td>114</td>
<td>11/06/2013</td>
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</table>
No evidence was identified pertaining to the diagnostic accuracy of cervical smear in patients with suspected cervix cancer where the clinical responsibility was retained by primary care.

References
Included studies
None

Excluded studies (with excl reason)
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
In Russian, not enough information can be extracted.
Narrative review
Not in PICO
Comment
Not in PICO
Narrative review
Not in PICO
Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO
Not in PICO

Narrative review

Not in PICO

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Not in PICO

Narrative review

Not in PICO

Not in PICO
Not in PICO
Not in PICO
Duplicate
Duplicate
Not in PICO
Narrative review
Narrative review
Narrative review
Narrative review
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Narrative review
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Narrative review

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Narrative review

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Narrative review

Narrative review
Narrative review

Narrative review

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Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
In Bulgarian, not enough information can be extracted, but I think it is "Not in PICO".
Not in PICO
Not in PICO
167-170.
Not in PICO

Not in PICO

Not in PICO

Not in PICO (secondary care)


endocervical glandular lesions. International Journal of Gynecological Pathology, 26: 71-75.
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
**Summary.** (5):1-6, 1999 Jan., 1-6.
Not in PICO (screening)


Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO
Not in PICO

Not in PICO


Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Ref Type: Generic

Ref ID: 145

Reprint: Not in File

Abstract: Examined breast self-examination (BSE) practices and cervical cancer Pap smear testing in female physicians. 284 female physicians (aged 24-67 yrs) residing in Norway completed questionnaires. Results show that 30.6% of Ss performed BSE at least once monthly; 54.6% of Ss had a Pap smear test once every 3rd yr at least. BSE was never practiced among 19.2% of the physicians: primary cited reasons for this included forgetting, membership in a low risk group, or having no symptoms of disease. 16.2% of Ss had never undergone routine Pap smears, claiming that they were in a low risk group, they had no symptoms of disease, they had a problem in finding a physician to attend, or they forgot. Compared with 738 Norwegian females, a subgroup of 135 physicians (aged 35-49 yrs) practiced BSE monthly or more often compared with other university educated women. However, a significantly lower percentage of the physicians had Pap smear tests every 3rd yr or more frequently. (PsycINFO Database Record (c) 2012 APA, all rights reserved)

Notes: DB - PsycINFO

AN - Peer Reviewed Journal: 2000-14380-006


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Sethom, F., Besbes, K. & Cammoun, M. (1989) For an early diagnosis of cervical cancer by systematic vaginal smears--clinical and psychological approach. [French]. *La Tunisie medicale*, 67: 505-511. In French, not enough information can be extracted/is reported to ascertain relevance (i.e., setting) for study 1; study 2 not in PICO


39: 36-43.
Not in PICO (secondary/tertiary care)
Not in PICO
Not in PICO
Not in PICO
Not in PICO
In Italian, limited information provided about patients, but I believe it is "Not in PICO"
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

**VULVAL CANCER**

**Review question:**
What is the risk of vulval cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
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Blair, A. R. and Casas, C. M. Gynecologic cancers. [Review] [45 refs]. Primary Care; Clinics in Office Practice 36[1], 115-130. 20-11-2009.  
Excl reason: Narrative review

Excl reason: Not in PICO

Bornstein, J., Pascal, B., Sova, Y., Rosenfeld, Y., and Abramovici, H. The vulvar clinic. [Hebrew]. Harefuah 119[12], 413-416. 16-12-1990.  
Excl reason: Not in PICO

Brannigan, J. and McCullough, A. Setting up a vulval clinic. Nursing Times 83[14], 30-32. 8-4-1987.  
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Candiani, P., Caru, A., Klingler, M., Campiglio, G. L., and Colonna, M. Vulvar dystrophy: The past and the present in the reconstructive treatment. [Italian]. Rivista Italiana di Chirurgia Plastica 23,
270-274. 1991.
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Door, A. Less common gynecologic malignancies. [Review] [90 refs]. *Seminars in Oncology Nursing* 18[3], 207-222. 2002.
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Fuller, A. F., Jr. Role of the primary physician in the detection and treatment of gynecologic cancer. Primary Care; Clinics in Office Practice 8[1], 111-129. 1981.
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Lundvall, F. [Early diagnosis of vulvar neoplasms]. [Danish]. Ugeskrift for Laeger
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Nauth, H. F. and Schilke, E. Cytology of the vulva, a morphological study in a large series. [German]. Geburtshilfe und Frauenheilkunde 42[10], 739-746. 1982.
Excl reason: Not in PICO

Excl reason: Narrative review

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Onnis, A., Marchetti, M., Maggino, T., and De, Toffoli J. Clinical experience in gynecological cancer management. b) Vulvar cancer: report from the Gynecologic Institutes of Padua University.
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van, der, V. Elderly patients with vulvar carcinoma: should we use standard treatment?. [Dutch]. Tijdschrift Voor Gerontologie En Geriatrie 28[6], 272-276. 1997. Excl reason: Not in PICO


van, Seters M., ten Kate, F. J., van, Beurden M., Verheijen, R. H., Meijer, C. J., Burger, M. P., and Helmerhorst, T. J. In the absence of (early) invasive carcinoma, vulvar intraepithelial neoplasia associated with lichen sclerosus is mainly of undifferentiated type: new insights in histology and aetiology. Journal of Clinical Pathology 60[5], 504-509. 2007. Excl reason: Not in PICO


Review question:
Which investigations of symptoms of suspected vulval cancer should be done with clinical responsibility retained by primary care?

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Study results

No evidence was identified pertaining to the diagnostic accuracy of biopsy in patients with suspected vulval cancer where the clinical responsibility was retained by primary care.

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Included studies

None

Excluded studies (with excl reason)


Not in PICO


Narrative review


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Narrative review

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Narrative review
VAGINA CANCER

Review question:
What is the risk of vagina cancer in patients presenting in primary care with symptom(s)?

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Excl reason: Not in PICO

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the female lower genital system (cervix uteri, vagina, vulva) established by the AGK (Colposcopy Work Group in the OGGG [Austrian Society of Gynecology and Obstetrics]). [German]. Gynakologisch-Geburtshilfliche Rundschat 41[3], 197-200. 2001.

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Rekhi, Bharat, Qureshi, Sajid, Basak, Ranjan, Desai, Sangeeta, Medhi, Seema, Kurkure, Purna, Menon, Santosh, Maheshwari, Amita, and Jambhekar, Nirmala. Primary vaginal Ewing's sarcoma or primitive neuroectodermal tumor in a 17-year-old woman: a case report. Journal of Medical Case Reports 4[1], 88. 2010.
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Review question:
Which investigations of symptoms of suspected vaginal cancer should be done with clinical responsibility retained by primary care?
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- # of studies included in qualitative synthesis: N = 0
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## Study results
No evidence was identified pertaining to the diagnostic accuracy of tests in patients with suspected vaginal cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)

Guideline


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


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Guideline


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de Mexico, 60: 55-59.
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PROSTATE CANCER

Review question:
What is the risk of prostate cancer in patients presenting in primary care with symptom(s)?

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<td>26/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 24
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP and the 5th study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Three of the studies also employed reference standards that are subject to an unclear risk of bias; all of which must be born in mind when evaluating the evidence contributed by these studies.
### Study results

#### Table 1: Prostate cancer: Single symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouwman (2007)</td>
<td>Urinary symptoms</td>
<td>Males aged ≥ 50 years</td>
<td>7.37 (5.5-10.7) 26/353</td>
</tr>
<tr>
<td>Deyo (1988)</td>
<td>Back pain</td>
<td>Male patients</td>
<td>0.13 (0.007-0.9) 1/750</td>
</tr>
<tr>
<td>Friedlander (2014)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>0.61 (0.36-1.03) 15/2455</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>1 (0.57-1.8) 33/1080</td>
</tr>
<tr>
<td></td>
<td>(reported twice)</td>
<td>All patients</td>
<td>1.6 (0.8-3.2)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Loss of weight</td>
<td>All patients</td>
<td>0.75 (0.38-1.4) 21/1080</td>
</tr>
<tr>
<td></td>
<td>(reported twice)</td>
<td>All patients</td>
<td>2.1 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Nocturia</td>
<td>All patients</td>
<td>2.2 (1.2-3.6) 49/1080</td>
</tr>
<tr>
<td></td>
<td>(reported twice)</td>
<td>All patients</td>
<td>3.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Hesitancy</td>
<td>All patients</td>
<td>3 (1.5-5.5) 21/1080</td>
</tr>
<tr>
<td></td>
<td>(reported twice)</td>
<td>All patients</td>
<td>2 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Rectal exam: Benign enlargement</td>
<td>All included patients</td>
<td>2.8 (1.6-4.6) 37/1080</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients 40-69 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients ≥ 70 years</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Frequency/urgency</td>
<td>All patients</td>
<td>2.2 (1.1-3.5) 77/1080</td>
</tr>
<tr>
<td></td>
<td>(reported twice)</td>
<td>All patients</td>
<td>3.1 (1.9-5.5)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Frequency</td>
<td>Patients 40-69 years</td>
<td>0.61 (NR)</td>
</tr>
<tr>
<td></td>
<td>Patients ≥ 70 years</td>
<td></td>
<td>7.4 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Retention</td>
<td>All patients</td>
<td>3.1 (1.5-6)</td>
</tr>
</tbody>
</table>
Cases: 18/217
Controls: 33/1080

* excluding 39 patients
with unsuspected cancer

1.6 (NR)

### Hamilton (2006)

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton (2006)</td>
<td>Impotence</td>
<td>All patients</td>
<td>3 (1.7-4.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Cases: 38/217</strong> Controls: 67/1080</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients 40-69 years</td>
<td>1.1 (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients ≥ 70 years</td>
<td>8.4 (NR)</td>
</tr>
</tbody>
</table>

When PSA was added to a small multivariate analysis (N = 208; N = 137 patients and N = 71 controls) with the following otherwise significant variables: urinary retention, second presentation with loss of weight, impotence, frequency, hesitancy, nocturia, haematuria, and rectal examination, these variables ceased to be significant predictors of prostate cancer while PSA > 4 ng/ml was significant (OR = 29, 95% CI 3.9-220; p = .001).

### Hallissey (1990)

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.08 (0.01-0.3)</td>
</tr>
</tbody>
</table>

CI = Confidence interval. *The authors report that a sub-analysis excluding the 39 patients who had previously unsuspected cancer identified at prostatectomy, showed that the PPVs of symptoms were little changed, other than for retention.

### Table 2: Prostate cancer: Symptom combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton (2006)</td>
<td>Haematuria + nocturia</td>
<td>All patients</td>
<td>1.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Haematuria + benign rectal exam</td>
<td>All patients</td>
<td>3.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Haematuria + malignant rectal exam</td>
<td>All patients</td>
<td>3.9 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Haematuria + frequency/urgency</td>
<td>All patients</td>
<td>1.8 (0.9-3.9)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Loss of weight + nocturia</td>
<td>All patients</td>
<td>12 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Loss of weight + frequency/urgency</td>
<td>All patients</td>
<td>1.8 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Nocturia + hesitancy</td>
<td>All patients</td>
<td>2.8 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Nocturia + benign rectal exam</td>
<td>All patients</td>
<td>3.9 (2.1-7.8)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Nocturia + malignant rectal exam</td>
<td>All patients</td>
<td>15 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Nocturia + frequency/urgency</td>
<td>All patients</td>
<td>3.2 (1.9-6)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Hesitancy + benign rectal exam</td>
<td>All patients</td>
<td>3.3 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Hesitancy + malignant rectal exam</td>
<td>All patients</td>
<td>10 (NR)</td>
</tr>
<tr>
<td>Hamilton (2006)</td>
<td>Hesitancy + frequency/urgency</td>
<td>All patients</td>
<td>4.7 (NR)</td>
</tr>
</tbody>
</table>
Hamilton (2006)  
**Benign rectal exam + frequency/urgency**  
All patients  
4 (2.3-7.4)

Hamilton (2006)  
**Malignant rectal exam + frequency/urgency**  
All patients  
13 (NR)

CI = Confidence interval.

**Evidence statement(s):**

The positive predictive values for prostate cancer of single symptoms presenting in a primary care setting ranged from 0.08% (for dyspepsia) to 12% (for malignant rectal exam; 5 studies, N = 7440). The studies were associated with 1-4 bias or applicability concerns (see also Table 1).

The positive predictive values for prostate cancer of symptom pairs presenting in a primary care setting ranged from 1.8% (for haematuria + frequency/urgency) to 15% (for nocturia + malignant rectal exam; 1 study, N = 1297). This study was a case-control study (i.e, high risk of bias for patient selection; see also Table 2).

**Evidence tables**

**Bouwman (2007)**

**PATIENT SELECTION**

A. risk of bias

Patient sampling  
Database study using data from the Registration Network Groningen (RNG) from 2003 and 2004, which is a database registering continuous automatic recorded data from, on average, 17 GPs working in practices in Groningen, Hoogeveen and Hoogezand-Sappemeer (population of approximately 30000 people) in the Netherlands.

Was a consecutive or random sample of patients enrolled?  
Unclear

Was a case-control design avoided?  
Yes

Did the study avoid inappropriate exclusions?  
Yes (probably)

Could the selection of patients have introduced bias?  
Unclear risk

B. Concerns regarding applicability

Patient characteristics and setting  
In the whole sample there were 4422 men aged ≥ 50 years in the period 2003 to 2004. Of these 353 men consulted the GP for urinary symptoms. No further details reported.

Inclusion criteria: Male patients aged ≥ 50 years in the period 2003 to 2004 who visited participating practices because of urinary symptoms (see “Index test” for further details) for the first time.

Exclusion criteria: None listed

Clinical setting: Primary care in the Netherlands.

Are there concerns that the included patients and setting do not match the review question?  
Unclear concern

**INDEX TEST**

A. Risk of bias

Index test  
The following ICPC codes were used: U01 (painful urination), U02 (increased urinary frequency / urgency), U04 (urinary incontinence), other micturition (U05) and Y06 (symptoms / complaints prostate) and some minor codes: U07
(other symptoms / complaints urine) and U13 (other symptoms / complaints bladder). The code Y85 for BPH / LUTS was not included in this selection because the RNG agreements apply to the use of the different parts of the ICPC. This agreement is that a health problem is initially registered as a symptom or complaint until by advancing knowledge and further research a diagnosis code may be added to the records.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

**NOTES**

Original paper is published in Dutch

**Deyo (1988)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for &lt; 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Neck pain.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>High concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Back pain; not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern  |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern  |

### FLOW AND TIMING

#### A. risk of bias
Flow and timing  | All the patients are accounted for in the results.
---|---
Was there an appropriate interval between index test and reference standard?  | Yes (probably)
Did all patients receive the same reference standard?  | Yes
Were all patients included in the analysis?  | Yes
Could the patient flow have introduced bias?  | Low risk

NOTES
It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Friedlander (2014)

PATIENT SELECTION

A. risk of bias

Patient sampling  | Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre’s (VUMC) Research Derivative, which is a “data repository that contains administrative and clinical information, including a complete record of visits and admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system” (p 634) located in Tennessee in the USA.
---|---
Was a consecutive or random sample of patients enrolled?  | Yes
Was a case-control design avoided?  | Yes
Did the study avoid inappropriate exclusions?  | Yes (probably)
Could the selection of patients have introduced bias?  | Low risk

B. Concerns regarding applicability

Patient characteristics and setting  | N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former smoker (N = 473), non-smoker (N = 1514).
---|---
Inclusion criteria: “Patients aged ≥ 40 years with a first diagnosis of hematuria” “between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC’s 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis.”
Exclusion criteria: “Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrites, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts;
prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic disease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystoscopy, cystectomy, ureteroscopy, nephrectomy, pyeloplasty, ureteral reimplantation.” We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their haematuria diagnosis (n = 3540, 53.8%).”

Clinical setting: Primary care, USA.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td></td>
</tr>
<tr>
<td>First diagnosis of haematuria” “by urinalysis (&gt;3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for haematuria (599.7, 599.70, 599.71 or 599.72)”</td>
<td></td>
</tr>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</strong></td>
<td>Low</td>
</tr>
</tbody>
</table>

| **REFERENCE STANDARD**                      |                |
| **A. risk of bias**                          |                |
| **Reference standard(s)**                   |                |
| The reference standard consisted checking the database for diagnoses of genitourinary neoplasms within 180 days after haematuria diagnosis, as determined by ICD-9 codes. | |
| **Is the reference standard likely to correctly classify the target condition?** | Unclear (is 180 days enough time to get a diagnosis of all cancers?) |
| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear (but all patients had a positive index test) |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Unclear risk |
| **B. Concerns regarding applicability**     |                |
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

| **FLOW AND TIMING**                         |                |
| **A. risk of bias**                          |                |
| **Flow and timing**                          |                |
| All patients appear to be accounted for. | |
| **Was there an appropriate interval between index test and reference standard?** | Yes |
| **Did all patients receive the same reference standard?** | Yes |
| **Were all patients included in the analysis?** | Yes |
| **Could the patient flow have introduced bias?** | Low risk |
There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

### Hallissey (1990)

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Propective consecutive patient series from a group of 10 general practices in England.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2585 aged &gt; 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care, England.</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

#### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Dyspepsia of any degree</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Upper gastrointestinal endoscopy within 4 weeks and follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |
### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>2659 patients were seen and 2585 attended for investigation</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatisis of unknown primary (7).

### Hamilton (2006)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Population-based case-control study, involving all 21 general practices in Exeter, Devon, UK.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

Attempts were made within the design or analysis to balance the comparison groups for potential confounders?

**For diagnostic case-control studies:**

The groups were comparable at baseline, including all major confounding and prognostic factors?

**Could the selection of patients have introduced bias?**

**High risk**

### B. Concerns regarding applicability

**Patient characteristics and setting**

**Cases:**

- 217 male patients; age at diagnosis: < 60 years: N = 15 (7%); 60-69 years: N = 51 (24%); 70-79 years: N = 100 (46%); ≥ 80 years: N = 51 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21).
- Controls:
  - 1080 male patients; age at diagnosis: < 60 years: N = 79 (7%); 60-69 years: N = 253 (23%); 70-79 years: N = 494 (46%); ≥ 80 years: N = 254 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21).

**Inclusion criteria:**

Cases: All patients aged 40 years or over with prostate cancer, diagnosed from 1998 to 2002 inclusive, were identified from the cancer registry at the Royal Devon and Exeter Hospital (the only hospital offering urological services to Exeter patients). Computerised searches at every practice identified any cases missing from the register. Cases without positive histology were included if the records contained a consultant urologist.
diagnosis of cancer based on strong clinical evidence. Controls: Five male controls were matched to each case on general practice and on age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria: Unobtainable records; no consultations in the 2 years before diagnosis; previous prostate cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>All entries into the primary care records for 2 years before diagnosis were coded, blinded to case/control status, using the International Classification of Primary Care-2. Only variables occurring in &gt;2.5% of cases or controls were analysed.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong> Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Prostate cancer code, from 1998 to 2002 inclusive, in the cancer registry at the Royal Devon and Exeter Hospital or the general practice records</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Could the patient flow have introduced bias?  
Low risk

NOTES

References

Included studies
Bouwman, I., Van Der Heide, W. K., Van Der Veen, W. J., and Van Der Meer, K. GPs and patients still think that lower urinary tract symptoms are an indication of prostate cancer. [Dutch]. Huisarts en Wetenschap 50[7], 321-325. 2007.

Excluded studies (with excl reason)

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Guideline


Not in PICO


Not in PICO


Narrative review


Oncology Nursing, 16: E26-E32.
Not in PICO
Bos, E. (2008) "It is not going to happen to me". Andros male clinic: A diagnostic center for typical male problems. [Dutch]. Pharmaceutisch Weekblad, 143: 30-34.
Narrative review
Not in PICO (referred population)
Narrative review
Not in PICO
Not in PICO
SR, but no studies conducted in primary care included
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review


**Duplicate**


Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO

Radiology, 14: 61-69.
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Lenk, V. S. (2005) [Diagnosis of the "aging male"--what is recommended?]. [Review] [27 refs] [German]. Urologe (Ausg.A), 44: 1167-1172.
Narrative review
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Symptoms not linked with cancers; analysis based on number of codes, not patients.
Symptoms not linked with cancers; analysis based on number of codes, not patients
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Mengus, C., Le, M. C., Trella, E., Yousef, K., Bubendorf, L., Provenzano, M., Bachmann, A., Heberer, M., Spagnoli, G. C. & Wyler, S. (2011) Elevated levels of circulating IL-7 and IL-15 in patients with
Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

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Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO

Paneesha, S., McManus, A., Arya, R., Scriven, N., Farren, T., Nokes, T., Bacon, S., Nieland, A., Cooper, D., Smith, H., O'Shaughnessy, D. & Rose, P. (2010) Frequency, demographics and risk (according to tumour type or site) of cancer-associated thrombosis among patients seen at outpatient DVT
Not in PICO (referred patients)

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (no symptoms per patient reported; population?)

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Systematic review. Relevant included studies are already included in our review.


Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO

Song, J. M., Kim, C. B., Chung, H. C. & Kane, R. L. (2005) Prostate-specific antigen, digital rectal examination and transrectal ultrasonography: A meta-analysis for this diagnostic triad of prostate...
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Narrative review
Narrative review
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review

Not in PICO

Not in PICO

Not in PICO

Guideline

Vasdev, N. & Thorpe, A. C. (2011) Has the introduction of the '2 week rule' in the UK led to an earlier diagnosis of urological malignancy? *eancermedicalsience*, 5.
Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Narrative review

Wei, J. T., Dunn, R. L., Litwin, M. S., Sandler, H. M. & Sanda, M. G. (2000) Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review
Narrative review

Not in PICO

Not in PICO

**Review question:**
Which investigations of symptoms of suspected prostate cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
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</thead>
<tbody>
<tr>
<td>Medline</td>
<td>1980-2013</td>
<td>3732</td>
<td>59</td>
<td>04/02/2013</td>
</tr>
<tr>
<td>Premedline</td>
<td>1980-2013</td>
<td>179</td>
<td>22</td>
<td>04/02/2013</td>
</tr>
<tr>
<td>Embase</td>
<td>1980-2013</td>
<td>1695</td>
<td>122</td>
<td>04/02/2013</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>1980-2013</td>
<td>139</td>
<td>15</td>
<td>31/01/2013</td>
</tr>
<tr>
<td>Psychinfo</td>
<td>1980-2013</td>
<td>73</td>
<td>3</td>
<td>04/02/2013</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>1980-2013</td>
<td>491</td>
<td>99</td>
<td>31/01/2013</td>
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<tr>
<td>Biomed Central</td>
<td>1980-2013</td>
<td>695</td>
<td>2</td>
<td>31/01/2013</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 317

**Update Search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>2013-26/08/2014</td>
<td>189</td>
<td>21</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Premedline</td>
<td>2013-26/08/2014</td>
<td>196</td>
<td>43</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Embase</td>
<td>2013-26/08/2014</td>
<td>179</td>
<td>42</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>2013-26/08/2014</td>
<td>38</td>
<td>0</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>2013-26/08/2014</td>
<td>76</td>
<td>14</td>
<td>26/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 84
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main risk of bias in this study pertains to the ca 20% of missing data in this study. It is not possible to ascertain whether these data are missing in a systematic manner and whether they are likely to substantially influence the test accuracy estimates provided by this study. The only applicability concern identified for this study concerns the underspecification of the patients, that is, it is not clear from the study whether all the patients were symptomatic patients presenting to primary care, and to the extent they are not from this patient group, the applicability to the current guideline is limited.

Study results
Table 1: Prostate cancer: PSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramachandran (1998)</td>
<td>PSA 4 ng/ml</td>
<td>54/582</td>
<td>88.9%</td>
<td>70%</td>
<td>False negativity rate = 11.1%</td>
</tr>
</tbody>
</table>
No evidence was found for MRI.

Evidence statement(s):

PSA testing (1 study, N = 582) conducted in patients presenting in a primary/hospital care setting is associated with sensitivities that ranged from 77.8-88.9%, specificities that ranged from 70-90.2% and false negativity rates that ranged from 11.1-22.2% for prostate cancer. The study was associated with one bias and one applicability concern (see also Table 1).

Evidence tables

Ramachandran (1998)

| PSA 5 ng/ml | 88.9% (NR) | 78% (NR) | False negativity rate = 11.1% |
| PSA 6 ng/ml | 87% (NR) | 82.6% (NR) | False negativity rate = 13% |
| PSA 7 ng/ml | 83.3% (NR) | 86% (NR) | False negativity rate = 16.7% |
| PSA 8 ng/ml | 83.3% (NR) | 88.3% (NR) | False negativity rate = 16.7% |
| PSA 9 ng/ml | 83.3% (NR) | 89% (NR) | False negativity rate = 16.7% |
| PSA 10 ng/ml | 77.8% (NR) | 90.2% (NR) | False negativity rate = 22.2% |

A. risk of bias
- Was a consecutive or random sample of patients enrolled? Yes
- Was a case-control design avoided? Yes
- Did the study avoid inappropriate exclusions? Yes
- Could the selection of patients have introduced bias? Low risk

B. Concerns regarding applicability
- Patient characteristics and setting: N = 582. No further detail reported.
  - Inclusion criteria: All patients who had a prediagnostic PSA estimation between August 1991 and December 1992 in the laboratory “Telepath” database. Unclear if they are all symptomatic and if they are all from primary care.
  - Exclusion criteria: None listed.
  - Clinical setting: Primary/hospital (?) care, England.

Are there concerns that the included patients and setting do not match the review question? Unclear concern

INDEX TEST
A. Risk of bias
Index test PSA
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Follow up for min 18 months using GP, Family Services Health Authority, hospice and hospital records</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern     |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>A total of 721 patients met the inclusion criteria. However, complete data were only available for 582 patients.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**NOTES**

2-by-2 tables cannot be extracted

**References**

**Included studies**


**Excluded studies (with excl reason)**


Not in PICO

(2005) Prostate specific antigen (PSA) near patient testing for diagnosis and management of prostate cancer (Structured abstract). Health Technology Assessment Database., 49.

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (screening)

Not in PICO

Not in PICO

Not in PICO (147/3470 received reference test)

Not in PICO

Not in PICO


Not in PICO


Narrative review


Not in PICO


Not available. Unlikely to be relevant (mass screening).


Guideline


Not in PICO


Not in PICO (38/71 patients had cancer)


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review/guideline

Bodelle, B., Naguib, N. N., Schulz, B., Eichler, K., Muller, C., Hansmann, M. L., Hammerstingl, R., Hubner, F., Vogl, T. J. & Zangos, S. (2013) 1.5-T magnetic resonance-guided transgluteal biopsies

Not in PICO

Boman, H. & Hedelin, H. (2005) Each fifth man above the age of 50 years who is referred to a urologist has cancer. PSA is important to get the priorities right. [Swedish]. *Lakartidningen*, 102: 1519-1521.

Not in PICO

Boman, H. & Hedelin, H. (2005) [One man of five aged 50 years and over referred to a urologist is diagnosed with cancer. PSA analysis is important for correct prioritization of the referrals]. [Swedish]. *Lakartidningen*, 102: 1519-1521.

Duplicate


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Duplicate

Not in PICO

Narrative review

Not in PICO

Narrative review

29: 403-406.
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Unclear if systematic review; no data synthesis; any relevant individual studies will be included separately.
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Cramer, R. & Dahm, F. J. (2005) [The follow-up of PSA tests for the early detection of prostate cancer. The responsibility of the physician to explain treatment methods which are not covered by public health insurance plans]. [German]. Urologe (Ausg.A), 44: 798-800.
Narrative review
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Duplicate

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO (not symptomatic population)


Not in PICO


Not in PICO


Not in PICO


Commentary

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO

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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO I believe (very little patient detail given but authors from "Servicio de Urologia" and cancer prevalence 25%).

Not in PICO

Not in PICO

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Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Iwamoto, H., Yumioka, T., Yamaguchi, N., Inoue, S., Masago, T., Morizane, S., Yao, A., Honda, M., Sejima, T. & Takenaka, A. (2014) The efficacy of target biopsy of suspected cancer lesions detected by magnetic resonance imaging and/or transrectal ultrasonography during initial prostate biopsies: Comparison of outcomes between two physicians. *Yonago Acta Medica, 57*:
Duplicate
Narrative review
Not in PICO
Not in PICO
Not in PICO
Cannot extract outcome in PICO (PPVs) as cancer data only reported in total for 10-year follow up
Not in PICO
Duplicate
Not in PICO
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Not in PICO
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Not in PICO
patients who could be adequately treated by focal therapy? Urologic Oncology, 30: 794-797.


Suspected Cancer: Appendix F (June 2015)
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (referred population)

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Lee, T. H. (2001) By the way, doctor... I can’t understand why there are reservations about the prostate-specific antigen (PSA) test. The "score" goes up when you have prostate cancer. So isn’t getting a PSA test a good way of catching prostate cancer early? But my doctor seems reluctant to order it. What’s the problem? *Harvard Health Letter*, 26: 8.

Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review

Not in PICO


Not in PICO (same data as other Lopez-Saez)


Not in PICO (same data as other Lopez-Saez)


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO
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Narrative review

Not in PICO

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Narrative review

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Narrative review
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Not in PICO

Duplicate

Not in PICO

Not available. WWS not conducted as unlikely to be relevant.


Not in PICO


Not in PICO
Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review


Not in PICO (referred patients; cancer rate 33.3%)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Suspected Cancer: Appendix F (June 2015)


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Narrative review


Narrative review


Guideline


Not in PICO


Not in PICO


Narrative review


Not in PICO (cancer prevalence rate = 25.4%)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

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Narrative review

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Not in PICO


Resonance Imaging, 35: 1414-1421.
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Duplicate
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Not in PICO
Not in PICO
Not in PICO
Not in PICO (44/260 received reference standard)


Narrative review
**BLADDER CANCER**

**Review question:**
What is the risk of bladder cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
<thead>
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<td>03/09/2012</td>
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<td>Premedline</td>
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<td>5</td>
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<td>Embase</td>
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<td>111</td>
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Total References retrieved (after de-duplication): 263

**Update Search**

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<td>68</td>
<td>3</td>
<td>11/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 26
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main bias and validity issues to note are that one study was conducted in a Belgian primary care population (Bruyninckx, 2003) and another in US primary care setting (Friedlander, 2014) and these studies are therefore only applicable to the extent that the populations are comparable to a UK GP population, another study (Hippisley-Cox 2012) only presented data for 967681 out of 1240722 eligible patients and it is unclear why, a third study (Jones, 2007) report the results for both 6 months and 3 years after first symptom presentation and it is unclear whether 3 years is too long an interval to be confident that the symptom is a result of underlying cancer, similarly, Friedlander (2014) only followed up the included patients for 180 days, which may be too short a time period. The final study (Shephard, 2012) employed a case-control design which has been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection.
Study results

Table 1: Bladder cancer: Meta-analyses

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
</table>

Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below.

Table 2: Bladder cancer: Individual positive predictive values from the meta-analyses

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruyninckx (2003)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>10.27 (7.6-13.7)                     42/409</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>4.35 (4.1-4.6)                       1645/37810</td>
</tr>
<tr>
<td>Friedlander (2014)</td>
<td>Haematuria</td>
<td>All included patients</td>
<td>1.34 (0.94-1.91)                     33/2455</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>6.48 (6.1-6.8)</td>
</tr>
</tbody>
</table>
Jones (2007, at 6 months) | Haematuria | All patients | 1201/18548
Jones (2007, at 3 years) | Haematuria | All patients | 4.2 (3.8-4.6) 466/11108

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria</td>
<td>Men (all ages)</td>
<td>14.2 (10.1-19.5)</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Haematuria</td>
<td>Men (all ages)</td>
<td>5.5 (5.2-5.8) 1262/22810</td>
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<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men (all ages) at 6 months</td>
<td>5.47 (4.9-6.1) 349/6385</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men (all ages) at 3 years</td>
<td>7.4 (6.8-8.1) 472/6385</td>
</tr>
<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria</td>
<td>Men &lt; 40 years</td>
<td>0 (0-12)</td>
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<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men &lt; 45 years at 3 years</td>
<td>0.99 (0.53-1.69) 13/1311</td>
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<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria</td>
<td>Men 40-59 years</td>
<td>3.6 (1.6-13.4)</td>
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<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men 45-54 years at 3 years</td>
<td>4.35 (3.11-5.9) 39/897</td>
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<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men 55-64 years at 3 years</td>
<td>8.51 (6.94-10.32) 94/1104</td>
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<tr>
<td>Bruyninckx (2003)</td>
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<td>Men &gt; 59 years</td>
<td>22.1 (15.8-30.1)</td>
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<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men 65-74 years at 3 years</td>
<td>11.21 (9.66-12.9) 170/1517</td>
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<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Men ≥ 85 years at 3 years</td>
<td>9.22 (6.43-12.7) 33/358</td>
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<tr>
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<td>Macroscopic haematuria</td>
<td>Women (all ages)</td>
<td>5.1 (2.5-9.8)</td>
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<td>Collins (2013)</td>
<td>Haematuria</td>
<td>Women (all ages)</td>
<td>2.6 (2.3-2.8) 383/15000</td>
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<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Women (all ages) at 6 months</td>
<td>2.48 (2.1-3) 117/4723</td>
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<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Women (all ages) at 3 years</td>
<td>3.4 (2.9-4) 162/4723</td>
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<td>Jones (2007)</td>
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<td>Women &lt; 45 years at 3 years</td>
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<td>Women 40-59 years</td>
<td>6.4 (1.7-18.6)</td>
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<td>Jones (2007)</td>
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<td>Women 45-54 years at 3 years</td>
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<tr>
<td>Jones (2007)</td>
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<td>Women 55-64 years at 3 years</td>
<td>3.42 (2.26-4.93) 27/790</td>
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<td>Women &gt; 59 years</td>
<td>8.3 (3.4-17.9)</td>
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<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Women 65-74 years at 3 years</td>
<td>5.91 (4.42-7.72) 50/846</td>
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<tr>
<td>Study (Year)</td>
<td>Symptom Description</td>
<td>Age Group</td>
<td>Relative Risk</td>
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<td>Haematuria</td>
<td>Women 75-84 years at 3 years</td>
<td>6.83 (5.06-8.98)</td>
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<td>Haematuria</td>
<td>Women ≥ 85 years at 3 years</td>
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<td>All patients &lt; 60 years</td>
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<td>Shephard (2012)</td>
<td>Visible haematuria (coded data only)</td>
<td>All patients 40-59 years</td>
<td>3.1 (1-9.8)</td>
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<td>Price (2014)</td>
<td>Visible haematuria (coded and uncoded data)</td>
<td>All patients 40-59 years</td>
<td>1.2 (0.64-2.3)</td>
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<tr>
<td>Shephard (2012)</td>
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<td>All patients ≥ 60 years</td>
<td>3.9 (3.5-4.6)</td>
</tr>
<tr>
<td>Price (2014)</td>
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<td>2.8 (2.5-3.1)</td>
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<tr>
<td>Bruyninckx (2003)</td>
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<td>All patients</td>
<td>5.3 (2.7-9.8)</td>
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<td>Men &gt; 60 years</td>
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<td>Non-visible haematuria + abdominal pain (coded and uncoded data)</td>
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<td>4.5 (NR)</td>
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<td>All patients</td>
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<td>Men &gt; 60 years</td>
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<tr>
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<td>Men &gt; 60 years</td>
<td>23.3 (16.3-32.1)</td>
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<td>All patients</td>
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<td>All patients</td>
<td>8.3 (5.8-11.5)</td>
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<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria without weight loss</td>
<td>Men &gt; 60 years</td>
<td>18.2 (12.4-26)</td>
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<tr>
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<td>All patients</td>
<td>20.8 (11-35.4)</td>
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<td>Men &gt; 60 years</td>
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<tr>
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<td>All patients</td>
<td>8.9 (6.2-12.4)</td>
</tr>
<tr>
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<td>Macroscopic haematuria without fatigue</td>
<td>Men &gt; 60 years</td>
<td>20.8 (14.2-29.4)</td>
</tr>
<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria with other symptoms</td>
<td>All patients</td>
<td>6.4 (4.3-9.3)</td>
</tr>
<tr>
<td>Bruyninckx (2003)</td>
<td>Macroscopic haematuria without other symptoms</td>
<td>All patients</td>
<td>3.9 (2.3-6.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Visible haematuria + constipation (coded data only)</td>
<td>All patients ≥ 60 years</td>
<td>2.7 (1.6-4.5)</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Symptoms组合</td>
<td>All patients ≥ 60 years</td>
<td>Odds Ratio (95% CI)</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Visible haematuria + constipation (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>2.2 (1.5-3.4)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Non-visible haematuria + constipation (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>2 (NR)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Visible haematuria + urinary tract infection (coded data only)</td>
<td>All patients ≥ 60 years</td>
<td>4.1 (3-6.2)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Visible haematuria + urinary tract infection (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>2.2 (1.8-2.8)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Non-visible haematuria + urinary tract infection (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>1.4 (0.8-2.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Visible haematuria + raised inflammatory markers (coded data only)</td>
<td>All patients ≥ 60 years</td>
<td>5.6 (NR as N &lt; 10)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Visible haematuria + raised inflammatory markers (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>3.3 (2-5.4)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Non-visible haematuria + raised inflammatory markers (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>1.25 (NR)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Visible haematuria + raised creatinine (coded data only)</td>
<td>All patients ≥ 60 years</td>
<td>5.1 (3.4-8.4)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Visible haematuria + raised creatinine (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>2.9 (2.1-3.9)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Non-visible haematuria + raised creatinine (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>1.1 (0.6-2.2)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Visible haematuria + raised white blood cell count (coded data only)</td>
<td>All patients ≥ 60 years</td>
<td>8.8 (NR as N &lt; 10)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Visible haematuria + raised white blood cell count (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>3.7 (2.1-6.3)</td>
</tr>
<tr>
<td>Price (2014)</td>
<td>Non-visible haematuria + raised white blood cell count (coded and uncoded data)</td>
<td>All patients ≥ 60 years</td>
<td>3.9 (NR)</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.11 (0.1-0.13)</td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Group</td>
<td>Cases</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------</td>
<td>--------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>284/253344</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain</td>
<td>All patients ≥ 60</td>
<td>187/105247</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>97/148097</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain (second attendance)</td>
<td>All patients ≥ 60</td>
<td>0.2 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + dysuria</td>
<td>All patients ≥ 60</td>
<td>0.4 (0.3-0.7)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + constipation</td>
<td>All patients ≥ 60</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + urinary tract infection</td>
<td>All patients ≥ 60</td>
<td>0.4 (0.3-0.6)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + raised inflammatory markers</td>
<td>All patients ≥ 60</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + raised creatinine</td>
<td>All patients ≥ 60</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Abdominal pain + raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria</td>
<td>All patients ≥ 60</td>
<td>0.7 (0.6-0.8)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria (second attendance)</td>
<td>All patients ≥ 60</td>
<td>1 (0.7-1.5)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria + constipation</td>
<td>All patients ≥ 60</td>
<td>0.5 (0.3-0.9)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria + urinary tract infection</td>
<td>All patients ≥ 60</td>
<td>0.7 (0.4-1.1)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria + raised inflammatory markers</td>
<td>All patients ≥ 60</td>
<td>0.9 (0.5-1.7)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria + raised creatinine</td>
<td>All patients ≥ 60</td>
<td>0.6 (0.4-1)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Dysuria + raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.9 (0.5-1.9)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Constipation</td>
<td>All patients ≥ 60</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Constipation (second attendance)</td>
<td>All patients ≥ 60</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Constipation + urinary tract infection</td>
<td>All patients ≥ 60</td>
<td>0.5 (0.3-0.7)</td>
</tr>
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</tr>
<tr>
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<td>Constipation + raised creatinine</td>
<td>All patients ≥ 60</td>
<td>0.3 (0.2-0.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Age Group</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shephard (2012)</td>
<td>Urinary tract infection</td>
<td>All patients ≥ 60</td>
<td>0.4</td>
<td>(0.3-0.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Urinary tract infection (second attendance)</td>
<td>All patients ≥ 60</td>
<td>0.5</td>
<td>(0.4-1.6)</td>
</tr>
<tr>
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<td>Urinary tract infection + raised inflammatory markers</td>
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</tr>
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<td>All patients ≥ 60</td>
<td>0.5</td>
<td>(0.3-0.6)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Urinary tract infection + raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.6</td>
<td>(0.4-0.9)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised inflammatory markers</td>
<td>All patients ≥ 60</td>
<td>0.1</td>
<td>(0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised inflammatory markers</td>
<td>All patients</td>
<td>0.18</td>
<td>(0.07-0.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised inflammatory markers + raised creatinine</td>
<td>All patients ≥ 60</td>
<td>0.3</td>
<td>(0.2-0.3)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised inflammatory markers + raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.2</td>
<td>(0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised creatinine</td>
<td>All patients ≥ 60</td>
<td>0.1</td>
<td>(0.12-0.14) As reported, but PPV or CI not reported correctly</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised creatinine</td>
<td>All patients</td>
<td>0.18</td>
<td>(0.3-0.6)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised creatinine + raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.3</td>
<td>(0.2-0.4)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised white blood cell count</td>
<td>All patients ≥ 60</td>
<td>0.2</td>
<td>(0.17-0.23)</td>
</tr>
<tr>
<td>Shephard (2012)</td>
<td>Raised white blood cell count</td>
<td>All patients</td>
<td>0.18</td>
<td>(0.07-0.4)</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Appetite loss</td>
<td>Women</td>
<td>0.1</td>
<td>(0.04-0.3)</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>0.18</td>
<td>(0.07-0.4)</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Weight loss</td>
<td>Women</td>
<td>0.1</td>
<td>(0.1-0.2)</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.41</td>
<td>(0.3-0.6)</td>
</tr>
<tr>
<td>Collins (2013)</td>
<td>Anaemia</td>
<td>All patients</td>
<td>0.6</td>
<td>(0.5-0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>1.4</td>
<td>(1.1-1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.3</td>
<td>(0.3-0.5)</td>
</tr>
</tbody>
</table>
NR = Not reported. Please note the calculations of the positive predictive values differ between the studies with Bruyninckx (2003), Hippisley-Cox (2012) and Jones (2007) using (TP)/(TP+FP) and Shephard (2012) using Bayesian statistics due to the case-control design of this study.

Evidence statement(s):

Haematuria (6 studies, N = 89345) presenting in a primary care setting is associated with overall positive predictive values ranging from 1.34%-10.27% for bladder cancer, which tended to be higher in men (5.47%-14.2%) than in women (2.48%-5.1%; 3 studies, total N = 49327) and to increase with age in men (up 22.1%; 2 studies, total N = 11517) and much less so in women (up to 8.53%; 2 studies, total N = 11517). All the studies were associated with 0-2 bias or applicability concern (see also Tables 1-3).

Haematuria in combination with other symptoms presenting in a primary care setting was associated with positive predictive values ranging from 1.1% (non-visible with raised creatinine in patients ≥ 60 years; 1 study, total N = 26633) to 33.3% (with weight loss in men > 60 years old; 1 study, total N = 409) for bladder cancer. Both studies were associated with 1 bias or applicability concern (see also Table 3).

Other symptoms (than haematuria) presenting alone or in combination with each other (but not haematuria) in a primary care setting were all associated with positive predictive values ≤ 1.5% for bladder cancer (3 studies, total N = 1284137). All the studies were associated with 0-1 bias or applicability concern (see also Table 3).

Evidence tables

Bruyninckx (2003)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: All patients complaining to their GP of macroscopic haematuria in 1993-1994 were included. Patients complaining repeatedly of</td>
</tr>
</tbody>
</table>
haematuria were included only once.
Exclusion criteria: None reported.
Clinical setting: Primary care, Belgium.

Are there concerns that the included patients and setting do not match the review question?
Unclear concern

INDEX TEST

A. Risk of bias

Index test
Haematuria was registered if a patient complained to the GP of any blood of urological origin that had not necessarily been checked by the GP during the study period, irrespective of the duration of the complaint and irrespective of the existence or absence of other signs or symptoms. Registered associated signs and symptoms were fatigue, weight loss, pain, nocturia, dysuria or frequency of micturition.

Were the index test results interpreted without knowledge of the results of the reference standard?
Yes

Could the conduct or interpretation of the index test have introduced bias?
Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?
Low concern

REFERENCE STANDARD

A. Risk of bias

Reference standard(s)
Diagnosis of urological cancer during a clinical follow-up of ≥ 18 months was registered as the reference standard. Urological cancer was defined as any malignancy of the urological tract that was confirmed histologically or by cystoscopy, intravenous pyelogram, or ultrasound scan. Recall letters were sent to the practices every six months, to check the included cases again upon the emergence of a diagnosis of any urological cancer. To ensure that all cases of urological cancer diagnosed within the follow-up period were identified, at the end of the period each of the GPs was sent a list of all their patients with macroscopic haematuria who were included in the study, in order to check for any ‘hidden’ urological cancer diagnosis.

Is the reference standard likely to correctly classify the target condition?
Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?
No (but all patients had a positive index test)

Could the reference standard, its conduct, or its interpretation have introduced bias?
Low risk

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?
Low concern

FLOW AND TIMING

A. Risk of bias

Flow and timing
All patients are accounted for in the results but the number of true negatives and false negatives could not be ascertained from the reported results.

Was there an appropriate interval between index test and reference standard?
Yes

Did all patients receive the same reference standard?
Yes
Collins (2013)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices.

**Symptoms:**

- Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women).

**Incident cases of renal tract cancer during the 2-year follow up period:**

N = 2283 (1685 men, 598 women).

**Inclusion criteria:**

- Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period.

**Exclusion criteria:**

- Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old.

**Clinical setting:** Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?**

Low concern

**INDEX TEST**

**A. Risk of bias**

**Index test**

‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk
### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference standard(s)</strong></td>
</tr>
<tr>
<td>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.</td>
</tr>
</tbody>
</table>

| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow and timing</strong></td>
</tr>
<tr>
<td>All patients seem to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

### NOTES

It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

### Friedlander (2014)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient sampling</strong></td>
</tr>
<tr>
<td>Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre’s (VUMC) Research Derivative, which is a “data repository that contains administrative and clinical information, including a complete record of visits and admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system” (p 634) located in Tennessee in the USA.</td>
</tr>
</tbody>
</table>

| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes (probably) |
| Could the selection of patients have introduced bias? | Low risk |

### B. Concerns regarding applicability

| Patient characteristics and N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former | |
Inclusion criteria: “Patients aged ≥ 40 years with a first diagnosis of hematuria” “between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC’s 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis.”

Exclusion criteria: “Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrites, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts: prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic disease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystoscopy, cystectomy, ureteroscopy, nephrectomy, pyeloplasty, ureteral reimplantation).” We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their hematuria diagnosis (n = 3540, 53.8%).”

Are there concerns that the included patients and setting do not match the review question? | Unclear concern
---|---

### INDEX TEST

#### A. Risk of bias

**Index test**

First diagnosis of hematuria” “by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72)".

**Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes
---|---

**Could the conduct or interpretation of the index test have introduced bias?** | Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**

The reference standard consisted checking the database for diagnoses of genitourinary neoplasms within 180 days after haematuria diagnosis, as determined by ICD-9 codes.

**Is the reference standard likely to correctly classify the target condition?** | Unclear (is 180 days enough time to get a diagnosis of all cancers?)
---|---

**Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear (but all patients had a positive index test)
### Could the reference standard, its conduct, or its interpretation have introduced bias?
- **Unclear risk**

### B. Concerns regarding applicability

#### Are there concerns that the target condition as defined by the reference standard does not match the question?
- **Low concern**

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

### NOTES
- There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

---

**Hippisley-Cox (2012)**

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). **Current symptoms and symptoms in the preceding year:** Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). **Incident cases of renal tract cancer during the 2-year follow up period:** N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; **Type of cancer:** Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2. **Inclusion criteria:** All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September... |
2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–C67).</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N =</td>
</tr>
</tbody>
</table>
70847), history of renal tract cancer (N = 1506), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

Was there an appropriate interval between index test and reference standard? Yes
Did all patients receive the same reference standard? Yes
Were all patients included in the analysis? No
Could the patient flow have introduced bias? High risk

**NOTES**

Please note, the included cancer cases were for renal tract cancer, not just bladder cancer.

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.

Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years.

Number of first occurrences in patients with no previous diagnosis of cancer:

- **Haematuria**: N = 11138, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females.
- **Haemoptysis**: N = 4822, mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: N = 10. Sex (of final sample): 2930 males, 1882 females.
- **Dysphagia**: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females.
- **Rectal bleeding**: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females.

Inclusion criteria: All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.

Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis
of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.

**Clinical setting:** Primary care

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding.</td>
</tr>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are there concerns that the index test, its conduct, or its interpretation differ from the review question?</strong></td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
</table>
| **Reference standard(s)** | Cancer code in the UK’s General Practice Research Database:  
Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs.  
Haemoptysis: Respiratory tract neoplasms.  
Dysphagia: Oesophageal neoplasms.  
Rectal bleeding: Colorectal neoplasms. |
| **Is the reference standard likely to correctly classify the target condition?** | Yes |
| **Were the reference standard results interpreted without knowledge of the results of the index tests?** | Unclear (but all patients had a positive index test) |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are there concerns that the target condition as defined by the reference standard does not match the question?</strong></td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow and timing</strong></td>
<td>All patients are accounted for in the results</td>
</tr>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Were all patients included in the analysis?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number...
expected from background incidence rates. Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:

Haematuria: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.

Dysphagia: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men.

Estimates based on the pre-specified cancers may be thus conservative for these symptoms.

Haemoptysis: Extension of the diagnostic criteria yielded 6 additional cancers.

Rectal bleeding: Extension of the diagnostic criteria yielded 2 additional cancers.

---

**Shephard (2012)/Price (2014)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>High risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

<table>
<thead>
<tr>
<th>Cases:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males: 3563 patients, median age at diagnosis = 73 (IQR = 65-80) years, median number of consultations = 14 (IQR = 9-22), UK.</td>
<td></td>
</tr>
<tr>
<td>Females: 1352 patients, median age at diagnosis = 75 (IQR = 67-82) years, median number of consultations = 15 (IQR = 10-23), UK.</td>
<td></td>
</tr>
<tr>
<td>Controls:</td>
<td></td>
</tr>
<tr>
<td>Males: 15452 patients, median age at diagnosis = 73 (IQR = 66-79) years, median number of consultations = 8 (IQR = 4-15), UK.</td>
<td></td>
</tr>
<tr>
<td>Females: 6266 patients, median age at diagnosis = 75 (IQR = 67-82) years, median number of consultations = 9 (IQR = 4-15), UK.</td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion criteria:**

Cases: Patients with a first record of bladder cancer between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a bladder cancer code was assigned the data of diagnosis/index date.
<table>
<thead>
<tr>
<th>Controls: Up to 5 controls were matched on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case. Exclusion criteria: Metastatic cancer of the bladder from a non-bladder primary, diagnosis before 2000, or no consultations in the year before diagnosis. Clinical setting: Primary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>A total of 29033 patients were identified, 24098 controls and 4935 cases. Of the controls the following exclusions were applied: bladder cancer post-2000 (N = 134), bladder control [?] pre-2000 (N = 125), metastatic cancer (N = 35), and no data in year pre-index date (N = 2086). Of the cases the following exclusions were applied: No controls (N = 13), metastatic cancer (N = 7).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were all patients included in the analysis?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the patient flow have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

### NOTES

43 symptoms and 104 abnormal test results were considered initially. 6 symptoms and 7 abnormal test variables were present in ≥ 5% of cases. The proportion of patients with a recorded fracture did not differ between cases (1.45%) and controls (1.46%).

The authors have published extra analyses of the same data in an additional paper (Price, 2014) wherein the data analysis is extended to the uncoded data in the CPRD, namely ‘free text’ notes added by GPs to augment a coded entry in a patient’s record. In particular, the authors “sought to identify whether there were sufficient additional non-visible haematuria entries to allow reliable estimates of its association with bladder cancer.”

### References

#### Included studies


Excluded studies (with excl reason)
Excl reason: Narrative review
Abbaszadeh, S., Taheri, S., and Nourbala, M. H. Bladder tumor in women with microscopic
hematuria: an Iranian experience and a review of the literature. Advances in Urology.:231861,
Excl reason: Not in PICO (secondary care)
Adeniyi, A. American Urological Association--94th annual meeting. 1-6 May 1999, Dallas, USA. Idrugs
2[7], 656-658. 1999.
Excl reason: Narrative review/meeting summary
Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Narrative review
tomography with multiplanar reformatted imaging and virtual cystoscopy in the early detection and evaluation of bladder carcinoma: comparison with conventional cystoscopy. Abdominal Imaging, 38: 184-192.
Not in PICO
Excl reason: Narrative review
Excl reason: Not in PICO
Excl reason: Not in PICO
Attallah, A. M., el-Didi, M., Seif, F., el-Mohamady, H., and Dalbagni, G. Comparative study between
Excl reason: Not in PICO
Banek, S., Schwentner, C., Tager, D., Pesch, B., Nasterlack, M., Leng, G., Gawrych, K., Bonberg, N.,
Johnen, G., Kluckert, M., Gakis, G., Todenoher, T., Hennenlotter, J., Bruning, T. & Stenzl, A.
Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Not in PICO

Published as abstract only. Not enough information can be extracted to ascertain the relevance of the study.

Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Guideline/narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Narrative review


Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Narrative review
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Excl reason: Not in PICO
Excl reason: Narrative review
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Narrative review
Excl reason: Not in PICO
Donohue, J. F. and Barber, N. J. How do we investigate haematuria and what role has finasteride? BJU International 93[1], 3-4. 2004.
Excl reason: Narrative review
Not in PICO
Excl reason: Narrative review


Elias, K., Svatek, R. S., Gupta, S., Ho, R., and Lotan, Y. High-risk patients with hematuria are not evaluated according to guideline recommendations. Cancer 116[12], 2954-2959. 15-6-2010.


Feil, G. and Stenzl, A. [Tumor marker tests in bladder cancer]. [Review] [60 refs] [Spanish]. Actas Urologicas Espanolas 30[1], 38-45. 2006.


Friedman, G. D., Hiatt, R. A., Quesenberry, C. P., Jr., Selby, J. V., and Weiss, N. S. Problems in assessing screening experience in observational studies of screening efficacy: example of
Excl reason: Not in PICO
Friedman, G. D., Carroll, P. R., Cattolica, E. V., and Hiatt, R. A. Can hematuria be a predictor as well as a symptom or sign of bladder cancer? Cancer Epidemiology, Biomarkers & Prevention 5[12], 993-996. 1996.
Excl reason: Not in PICO (screening population w/o symptoms, risk based analyses, setting?)
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
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Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Narrative review

Excl reason: Guideline

Hall, C. L. The patient with haematuria. The Practitioner 243[1600], 564-571. 5-7-0568.
Excl reason: Narrative review

Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

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Excl reason: Not in PICO
Excl reason: Narrative review
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Excl reason: Not in PICO
Excl reason: Not in PICO
Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Narrative review
Jimbo, M. Evaluation and management of hematuria. [Review]. Primary Care; Clinics in Office Practice 37[3], 461-472. 20-11-2010.
Excl reason: Narrative review
Excl reason: Not in PICO
Excl reason: Not in PICO
Kajita, Y., Megumi, Y., and Okabe, T. [Renal carcinoid tumor presenting as bladder tamponade: a case report and review of the Japanese cases]. [Review] [10 refs] [Japanese]. Hinyokika Kiyo -


Kjaer, S. K., Knudsen, J. B., Sorensen, B. L., and Moller, Jensen O. The Copenhagen case-control study of bladder cancer. V. Review of the role of urinary-tract infection. [Review] [33 refs]. Acta
Excluded reason: Not in PICO (risk, not symptoms)

Excluded reason: Not in PICO

Kohler, C. and Varenhorst, E. Microscopic hematuria in adults--a diagnostic dilemma. Scientific guidelines for management are not available according to a review of the literature. [Swedish]. Lakartidningen 96[45], 4911-4916. 10-11-1999.
Excluded reason: Not in PICO (mixed population that cannot be disentangled)

Excluded reason: Not in PICO

Excluded reason: Not in PICO

Not in PICO

Excluded reason: Not in PICO

Excluded reason: Not in PICO

Excluded reason: Not in PICO

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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Narrative review

Excl reason: Not in PICO

Not in PICO

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Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

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Excl reason: Not in PICO

Not in PICO

Excl reason: Not in PICO

Mobley, D. F. and Baum, N. Interstitial cystitis. When urgency and frequency mean more than routine inflammation. [Review] [16 refs]. Postgraduate Medicine 99[5], 201-204. 207.
Excl reason: Narrative review

Excl reason: Not in PICO
Suspected Cancer: Appendix F (June 2015)

Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Narrative review


Excl reason: Narrative review


Excl reason: Not in PICO


Excl reason: Not in PICO


Excl reason: Not in PICO


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Excl reason: Not in PICO


Not in PICO


Excl reason: Not in PICO


Not in PICO


Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Parsons, B. A., Evans, S., and Wright, M. P. Prostate cancer and urinary incontinence. [Review] [70 refs]. *Maturitas* 63[4], 323-328. 20-8-2009.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

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Excl reason: Narrative review
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Excl reason: Not in PICO
Systematic review, checked for relevant studies
Excl reason: Not in PICO
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Excl reason: Not in PICO
Narrative review
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Narrative review

Excl reason: Not in PICO

Not in PICO (setting)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Simon, J., Bartsch, G., Jr., Rinnab, L., Hautmann, R. E., and Volkmer, B. G. Transrectal ultrasound as diagnostic tool for the detection of local recurrence following cystectomy and urinary diversion.


Excl reason: Not in PICO
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Excl reason: Not in PICO
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Excl reason: Not in PICO
Thiruchelvam, N. and Mostafid, H. Do patients with frank haematuria referred under the two-week rule have a higher incidence of bladder cancer? Annals of the Royal College of Surgeons of England 87[5], 345-347. 2005.
Excl reason: Not in PICO
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Excl reason: Not in PICO
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Institute 95[16], 1211-1218. 20-8-2003.
Excl reason: Not in PICO

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Excl reason: Not in PICO

Not in PICO

Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO (secondary care)

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Narrative review

Excl reason: Not in PICO

Review question:
Which investigations of symptoms of suspected bladder cancer should be done with clinical responsibility retained by primary care?

Results

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Study results

No evidence was identified pertaining to the diagnostic accuracy of urine cytology, ultrasound, cystoscopy, blood HCG, urine marker NMP22, and urine marker MCM5 in patients with suspected bladder cancer where the clinical responsibility was retained by primary care.

References

Included studies

None

Excluded studies

  Narrative review
  Not in PICO
  Not in PICO
  Not in PICO
  Not in PICO
Imaging, 38: 184-192.
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Narrative review

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Not in PICO

Not in PICO

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Narrative review

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Not in PICO

Duplicate

Narrative review

Narrative review

Narrative review
Narrative review

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Not in PICO

Not in PICO

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Narrative review

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Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO
Not in PICO

Not in PICO

In Japanese. No translation available.

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

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Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (secondary care)

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Systematic review, checked for relevant studies

Narrative review

Not in PICO

Not in PICO

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Narrative review

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Narrative review
Not in PICO (at least 17/27 had cancer)
Not in PICO
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Narrative review
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Not in PICO
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Narrative review

Narrative review

Narrative review

Narrative review

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Not in PICO

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Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO
## RENAL CANCER

**Review question:**
What is the risk of renal cancer in patients presenting in primary care with symptom(s)?

### Results

#### Literature search

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#### Update Search

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Total References retrieved (after de-duplication): 22
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that patient selection is associated with a number of bias or applicability concerns in most of the included studies, with some studies employing non-consecutive or non-random selection of patients and with some studies being employed in settings that are not clearly directly representative of UK-based primary care. Other areas of concern include missing data, compromised reference standards and underspecified presenting symptoms. These issues should all be born in mind when evaluating the evidence along with the fact that a large number of the included cancers were not renal cancers.
### Study results

#### Table 1: Renal cancer: Meta-analyses

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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<tbody>
<tr>
<td>Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 6 months)</td>
<td>Haematuria</td>
<td>All patients (N = 69921)</td>
<td>3.05 (1.3-7.01)</td>
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<tr>
<td>Collins (2013), Friedlander (2014), Hippisley-Cox (2012), Jones (2007, at 3 years)</td>
<td>Haematuria</td>
<td>All patients (N = 69921)</td>
<td>3.3 (1.35-7.84)</td>
</tr>
</tbody>
</table>

*Please note that the data from Shephard (2012) are not included in these meta-analyses due to the case-control design of the study. These data are instead reported in the table below.*

#### Table 2: Renal cancer: Individual positive predictive values from the meta-analyses

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value, % (95% CI)</th>
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<tbody>
<tr>
<td>Collins (2013)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>4.35 (4.1-4.6)</td>
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<td></td>
<td></td>
<td>1645/37810</td>
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<tr>
<td>Friedlander (2014)</td>
<td>Haematuria</td>
<td>All included patients</td>
<td>0.65 (0.39-1.83)</td>
</tr>
<tr>
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<td></td>
<td>16/2455</td>
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<tr>
<td>Hippisley-Cox (2012)</td>
<td>Haematuria</td>
<td>All patients</td>
<td>6.48 (6.1-6.8)</td>
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</table>
Table 3: Renal cancer: Patients aged > 14 years: Single symptoms

<table>
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<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
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<tbody>
<tr>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.11 (0.1-0.13) 284/253344</td>
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<tr>
<td></td>
<td></td>
<td>Men</td>
<td>0.2 (0.2-0.21) 187/105247</td>
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<tr>
<td></td>
<td></td>
<td>Women</td>
<td>0.1 (0.1-0.1) 97/148097</td>
</tr>
<tr>
<td>Hippisley-Cox (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.2 (0.2-0.2) 182/93077</td>
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<tr>
<td>Muris (1995)</td>
<td>Non-acute abdominal complaints</td>
<td>All patients</td>
<td>0.11 (0.01-0.7) 1/933</td>
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<tr>
<td>Shephard (2013)</td>
<td>Abdominal pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Abdominal pain: 2 presentations</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.08-0.11)</td>
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<tr>
<td>Shephard (2013)</td>
<td>Constipation: 2 presentations</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.06-0.12)</td>
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<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infection</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.09-0.12)</td>
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<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infection: 2 presentations</td>
<td>Patients ≥ 60 years</td>
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<td>Shephard (2013)</td>
<td>Fatigue</td>
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</tr>
<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Women 75-84 years at 3 years</td>
<td>6.83 (5.06-8.98) 47/688</td>
</tr>
<tr>
<td>Jones (2007)</td>
<td>Haematuria</td>
<td>Women ≥ 85 years at 3 years</td>
<td>8.53 (5.6-12.3) 25/293</td>
</tr>
</tbody>
</table>

TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 4: Renal cancer: Patients aged ≥ 60 years: Symptom combinations
<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Condition 1 and Condition 2</th>
<th>Patient Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and lower urinary tract infections</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and fatigue</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and raised inflammatory markers</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.5)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Constipation and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.6 (NR)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and lower urinary tract infections</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and fatigue</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and raised inflammatory markers</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Back pain and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infections and fatigue</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infections and nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.4)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infections and raised inflammatory markers</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infections and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (0.2-0.4)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Lower urinary tract infections and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Fatigue and nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.1-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Fatigue and raised inflammatory markers</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Fatigue and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.5 (0.3-0.9)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Fatigue and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.2-0.8)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Nausea and raised inflammatory markers</td>
<td>Patients ≥ 60 years</td>
<td>0.2 (0.2-0.3)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Nausea and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.2-0.6)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Nausea and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.5 (NR)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Raised inflammatory markers and thrombocytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.4 (0.3-0.5)</td>
</tr>
<tr>
<td>Shephard (2013)</td>
<td>Raised inflammatory markers and microcytosis</td>
<td>Patients ≥ 60 years</td>
<td>0.7 (0.5-1)</td>
</tr>
</tbody>
</table>
NR = Not reported. TP = True positives, FP = False positives. Shephard (2013) calculated the positive predictive values using Bayesian statistics.

Table 5: Renal cancer: Positive predictive values for any childhood cancer: All patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.07 (0.064-0.078) Cases: 427/1267 Control: 829/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Neurological symptoms 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.083 (0.067-0.105) Cases: 108/1267 Control: 207/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Headache 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.064 (0.051-0.082) Cases: 90/1267 Control: 224/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Headache 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.06 (0.04-0.08) Cases: 73/1267 Control: 55/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Headache 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td>0.13 (0.08-0.22)</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lymphadenopathy 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.096 (0.074-0.126) Cases: 82/1267 Control: 136/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.09 (0.06-0.13) Cases: 69/1267 Control: 33/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All included patients</td>
<td>0.2 (0.1-0.39)</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lump/mass/swelling 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.172 (0.119-0.25) Cases: 56/1267 Control: 52/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.11 (0.06-0.2) Cases: 42/1267 Control: 16/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td>0.3 (0.09-0.99)</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Fatigue 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.085 (0.06-0.121) Cases: 47/1267 Control: 88/15318</td>
</tr>
<tr>
<td>Author</td>
<td>Condition</td>
<td>Reference Period</td>
<td>Participants</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Fatigue 0-12 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Fatigue 0-12 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Back pain 0-12 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Bruising 0-12 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Bruising 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Pallor 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Pallor 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Abnormal movement 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Bleeding 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Bleeding 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Visual symptoms 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All included patients</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All included patients</td>
<td></td>
</tr>
</tbody>
</table>
### Table 6: Renal cancer: Positive predictive values for any childhood cancer: Patients aged 0-4 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-3 months before diagnosis</td>
<td>Patients aged 0-4 years</td>
<td>0.081 (0.059-0.112)</td>
<td>Cases: 96/436 Control: 55/4802</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Pain 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td>0.14 (0.07-0.31)</td>
<td>Cases: 42/1267 Control: 41/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.04 (0.03-0.07)</td>
<td>Cases: 107/1267 Control: 102/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All included patients</td>
<td>0.13 (0.08-0.19)</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.266 (0.117-0.609)</td>
<td>Cases: 15/1267 Control: 9/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>≥ 3 consultations</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Childhood infection 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.04 (0.03-0.07)</td>
<td>Cases: 54/1267 Control: 236/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Urinary symptoms 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>0.04 (0.03-0.07)</td>
<td>Cases: 14/1267 Control: 9/15318</td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Vomiting 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Cough 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Rash 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Abdominal pain 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Abdominal mass 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Fever 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Eye swelling 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Shortness of breath 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013)</td>
<td>Constipation 0-3 months before diagnosis</td>
<td>All included patients</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Hepatosplenomegaly 0-12 months before diagnosis</td>
<td>All included patients</td>
<td>2.19 (0.295-17.034)</td>
<td>Cases: 14/1267 Control: 1/15318</td>
</tr>
</tbody>
</table>

The positive predictive values are calculated using Bayesian statistics.
The positive predictive values are calculated using Bayesian statistics.

Table 7: Renal cancer: Positive predictive values for any childhood cancer: Patients aged 5-14 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-3 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.056 (0.047-0.068) Cases: 246/831 Control: 156/10516</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.075 (0.066-0.084) Cases: 303/831 Control: 581/10516</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Neurological symptoms 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.091 (0.067-0.123) Cases: 65/831 Control: 102/10516</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Headache 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.055 (0.043-0.07) Cases: 82/831 Control: 213/10516</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lymphadenopathy 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.118 (0.085-0.164) Cases: 62/831 Control: 75/10516</td>
</tr>
</tbody>
</table>
The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

Patients aged > 14 years

Haematuria (5 studies, N = 87161) presenting in a primary care setting is associated with overall positive predictive values of 0.65-6.48% for renal cancer, which tended to be higher in men (5.47-5.5%) than in women (2.48-2.6%; 2 studies, N = 48918) and to increase with age in men (up to 11.21%; 1 study, N = 11108) and less so in women (up to 8.53%; 1 study, N = 11108). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers. Each of the studies was associated with 0-2 bias concern (see also Tables 1-3).

For renal cancer the positive predictive values of single symptoms (excluding haematuria; 6 studies, N = 344897) presenting in primary care ranged from 0.05% (for back pain) to 1.4% (for anaemia in men). The evidence was, however, compromised by a large number of the included cancers being non-renal cancers and ≤ 3 bias or applicability concerns associated with 4 of the 6 included studies (see also Table 3).

For renal cancer the positive predictive values of symptom combinations (1 study, N = 17240) presenting in primary care ranged from 0.1% (for constipation in combination with either abdominal pain, nausea or lower urinary tract infection) to > 5% (for abdominal pain combined with microcytosis). The included study was associated with 1 bias concern (see also Table 4).

Patients aged < 15 years

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for 'lump/mass/swelling' [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for patients aged 5-14 years old (all from 1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 5-7).
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

**Patient characteristics and setting**

A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices.

**Symptoms:**
- Haemoglobin $< 11$ g/dl recorded in the last year ($N = 16961$; 3969 men, 12992 women), abdominal pain ($N = 253344$; 105247 men, 148097 women), appetite loss ($N = 6097$; 2616 men, 3481 women), weight loss ($N = 29369$; 13332 men, 16037 women), haematuria ($N = 37810$; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry ($N = 49303$; 18130 men, 31173 women).
- **Incident cases of renal tract cancer during the 2-year follow up period:** $N = 2283$ (1685 men, 598 women).

**Inclusion criteria:**
- Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period.

**Exclusion criteria:**
- Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, $< 30$ years old or $\geq 85$ years old.

**Clinical setting:** Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?** Low concern

### INDEX TEST

#### A. Risk of bias

**Index test**

‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes

**Could the conduct or interpretation of the index test have introduced bias?** Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

#### A. risk of bias

**Reference**

Renal tract cancer, which was defined as incident diagnosis of cancer of the
standard(s) | bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.

| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

A. risk of bias

| Flow and timing | All patients seem to be accounted for |
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| Could the patient flow have introduced bias? | Low risk |

NOTES

It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

Deyo (1988)

PATIENT SELECTION

A. risk of bias

| Patient sampling | Prospective consecutive? patient series |
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes (probably) |
| Could the selection of patients have introduced bias? | Unclear risk |

B. Concerns regarding applicability

Patient characteristics and setting

N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%).

Inclusion criteria: Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint.

Exclusion criteria: Neck pain.

Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.
<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>High concern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>Back pain; not further specified.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All the patients are accounted for in the results.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple</td>
</tr>
</tbody>
</table>
myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Dommett (2012, 2013)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics and setting</strong></td>
</tr>
<tr>
<td><strong>Cases:</strong></td>
</tr>
<tr>
<td>Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132.</td>
</tr>
<tr>
<td><strong>Controls:</strong></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
</tr>
<tr>
<td>Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.</td>
</tr>
<tr>
<td>Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date).</td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
</tr>
<tr>
<td><strong>Clinical setting:</strong> Primary care, UK.</td>
</tr>
<tr>
<td><strong>Are there concerns that the included patients and setting do not match the review question?</strong></td>
</tr>
</tbody>
</table>
### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>The GPRD uses just over 100,000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. <strong>No more information reported.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Cancer diagnosis in the UK’s General Practice Research Database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

<table>
<thead>
<tr>
<th>This study is published in two papers.</th>
</tr>
</thead>
</table>

### Friedlander (2014)

### PATIENT SELECTION

#### A. Risk of bias

| Patient sampling | Retrospective cohort study, using claims data and laboratory values from the Vanderbilt University Medical Centre’s (VUMC) Research Derivative, which is a “data repository that contains administrative and clinical information, including a complete record of visits and |
admissions, laboratory data, and diagnosis and procedure codes, on every patient treated in the Vanderbilt health system” (p 634) located in Tennessee in the USA.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

**Patient characteristics and setting**

N = 2455 patients, 724 males / 1731 females, median (inter-quartile range) age = 58 (49-68) years; smoking history: current smoker (N = 406), former smoker (N = 473), non-smoker (N = 1514).

**Inclusion criteria:** “Patients aged ≥ 40 years with a first diagnosis of hematuria” “between 2004 and 2012 by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72) at one of the VUMC’s 19 primary care clinics. To be included in the study, patients must have had records for 1 year before the date of hematuria diagnosis.”

**Exclusion criteria:** “Patients were excluded if they had a urinary tract infection (defined as a urinalysis positive for both leukocyte esterase and urine nitrates, or a positive urine culture) within 4 weeks before or 1 week after the index hematuria episode (n = 590, 9.0%) or had a prior explanatory diagnoses and procedures that would preclude the need for a hematuria evaluation (according to a convened panel of content experts; prostate/renal/bladder/other cancer, benign prostate/renal/bladder/other mass, prostate dysplasia, cystitis, urethritis, epididymitis/orchitis, prostatitis, pyelonephritis, urolithiasis, prostatic enlargement, trauma, medical renal disease, haematologic/thrombotic disease?, anatomic abnormality, prostatectomy, prostate biopsy, transurethral incision of prostate, resection of prostate, cystectomy, cystectomy, ureteroscopy, nephrectomy, pyeloplasty, ureteral reimplantation).” We then used Physicians Current Procedural Terminology Coding System, 4th Edition and ICD-9 codes to exclude patients with an explanatory diagnosis or procedure within 180 days preceding their hematuria diagnosis (n = 3540, 53.8%).”

**Clinical setting:** Primary care, USA.

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

### INDEX TEST

**A. Risk of bias**

**Index test**

First diagnosis of hematuria” “by urinalysis (>3 red blood counts per high power field) or International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes for hematuria (599.7, 599.70, 599.71 or 599.72)”.

**Were the index test results interpreted without knowledge of the results of the reference standard?**

Yes

**Could the conduct or interpretation of the index test have introduced bias?**

Low risk

### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low
REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

NOTES

There were 66 patients with cancer: Bladder (N = 33), renal cell (N = 16), prostate (N = 15). The types of cancer for the remaining two cases were not reported.

Hippisley-Cox (2012)

PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).</td>
</tr>
<tr>
<td>Current symptoms and symptoms in the preceding year:</td>
</tr>
<tr>
<td>Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin &lt; 11 g/dl in the last year (N = 16169).</td>
</tr>
<tr>
<td>Incident cases of renal tract cancer during the 2-year follow up period:</td>
</tr>
</tbody>
</table>
N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

Are there concerns that the included patients and setting do not match the review question? | Low concern
---|---

INDEX TEST

A. Risk of bias

Index test
‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes
---|---

Could the conduct or interpretation of the index test have introduced bias? | Low risk
---|---

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern
---|---

REFERENCE STANDARD

A. Risk of bias

Reference standard(s)
Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).

Is the reference standard likely to correctly classify the target condition? | Yes
---|---

Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear
---|---

Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk
---|---
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

**Jones (2007)**

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Retrospective consecutive patient series using patients in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
<td>A total of 923605 patients were identified, of whom 762325 were aged ≥ 15 years. Number of first occurrences in patients with no previous diagnosis of cancer: Haematuria: N = 11108, mean (SD) age at first symptom = 58.5 (18.9) years. Patients excluded due to incomplete dates for their first symptom: N = 30. Sex (of final sample): 6385 males, 4723 females. Haemoptysis: N = 4822, mean (SD) age at first symptom = 61.6 (18) years. Patients excluded due to incomplete dates for their first symptom: N = 10. Sex (of final sample): 2930 males, 1882 females. Dysphagia: N = 6003, mean (SD) age at first symptom = 54.5 (19.4) years. Patients excluded due to incomplete dates for their first symptom: N = 4. Sex (of final sample): 2628 males, 3371 females. Rectal bleeding: N = 15314, mean (SD) age at first symptom = 52.5 (18.8) years. Patients excluded due to incomplete dates for their first symptom: N = 25. Sex (of final sample): 7523 males, 7766 females.</td>
</tr>
</tbody>
</table>

---

Suspected Cancer: Appendix F (June 2015)  
Page 1017 of 1735
Inclusion criteria:
All patients from 128 general practices that provided data of a sufficient standard from 1 January 1994 to 31 December 2000 and which provided exclusively Read coded data, who were aged between 15 and 100 years, whose first ever recorded occurrence of each alarm symptom (haematuria, haemoptysis, dysphagia, or rectal bleeding) was after 31 December 1994 and who had not previously been diagnosed as having any cancer.

Exclusion criteria: Patients whose date of first symptom or first relevant diagnosis of cancer was before 1 January 1995 and patients with a diagnosis of any other cancer than the ones of interest before the date of the first recorded symptom or before the index cancer diagnosis date if the related symptom was not recorded.

Clinical setting: Primary care

Are there concerns that the included patients and setting do not match the review question? | Low concern
---|---

### INDEX TEST

#### A. Risk of bias

| Index test | Identification of all patients who ever had symptoms recorded for haematuria, haemoptysis, dysphagia, or rectal bleeding. |
---|---|

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

#### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

| Reference standard(s) | Cancer code in the UK’s General Practice Research Database (the authors report cancer diagnosis at two time points, namely in the first 6 months and 3 years after the first alarm symptom):
Haematuria: Urinary tract neoplasms, including neoplasms of the urethra, bladder, ureter, and kidney but excluding neoplasms of the prostate and other reproductive organs.
Haemoptysis: Respiratory tract neoplasms.
Dysphagia: Oesophageal neoplasms.
Rectal bleeding: Colorectal neoplasms. |
---|---|

| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear (but all patients had a positive index test) |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

#### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

### Flow and timing

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients are accounted for in the results</td>
<td></td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

- Diagnoses of cancer were most often made in the first three months after the onset of alarm symptoms; very few diagnoses of cancer were made later than three years after symptom onset. In the 4th and 5th years of study, the small number of observed occurrences of cancer was similar to the number expected from background incidence rates.
- Secondary analyses evaluating whether the incidence of neoplasms other than those prespecified was increased after the occurrence of alarm symptoms showed for:
  - **Haematuria**: Inclusion of cancers of the reproductive organs yielded 21 additional cancers in women and 158 cancers in men, mostly cancers of the prostate. Inclusion of these cancers in the analysis would give a positive predictive value of 3.9% in women and 9.9% in men.
  - **Dysphagia**: Inclusion of gastric cancers yielded 17 additional cancer diagnoses in women and 30 in men. Inclusion of these cancers gave positive predictive values of 5.2% in women and 6.9% in men.
  - *Estimates based on the pre-specified cancers may be thus conservative for these symptoms.*
  - **Haemoptysis**: Extension of the diagnostic criteria yielded 6 additional cancers.
  - **Rectal bleeding**: Extension of the diagnostic criteria yielded 2 additional cancers.

---

### Muris (1995)

#### PATIENT SELECTION

##### A. risk of bias

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series from 80/460 general practitioners in Limburg (Holland)</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

##### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 933; 335 males, 598 females; age range = 18-75, aged &gt; 30 years: N = 712, aged &gt; 40 years: N = 517, aged &gt; 60 years: N = 171.</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Patients who in 1989 consulted one of the participating GPs for new abdominal complaints lasting ≥ 2 weeks and with whom the GPs had a diagnostic problem.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None listed.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>GPs in Holland</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>High concern</td>
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</tbody>
</table>

---

### INDEX TEST
<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>New abdominal complaints lasting $\geq$ 2 weeks. Not further specified.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>High concern</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REFERENCE STANDARD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Follow up for $\geq$ 12 months (mean = 18 months).</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLOW AND TIMING</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

| NOTES | Other cancers diagnosed in these patients were: Stomach (2/933), pancreas (2/933), trachea/bronchus/lung (2/933), colorectal (4/933), cervix (1/933), other cancer of the female genital system (2/933), and other and unspecified sites (2/933). |

Oudega (2006)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective study of all primary care physicians (N = 50) within a catchment area (ca 130000 inhabitants) of a non-teaching hospital in Holland.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

| B. Concerns regarding applicability |  |
### Patient characteristics and setting

N = 430; 162 males, 268 females; mean age (SD) = 60.7 (18.2) years.

**Inclusion criteria:** Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis.

**Exclusion criteria:** Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis.

**Clinical setting:** Primary care, Holland.

### Are there concerns that the included patients and setting do not match the review question?

**Unclear concern**

### INDEX TEST

#### A. Risk of bias

**Index test**

Deep vein thrombosis (suspicion based on painful swollen leg ≤ 30 days). Patients were classified as having secondary deep vein thrombosis if ≥ 1 of the following risk factors for deep vein thrombosis were present: Recent surgery, prolonged immobilisation, use of oral contraceptives or hormonal replacement therapy. If no risk factors were present patients were classified as having idiopathic deep vein thrombosis.

**Were the index test results interpreted without knowledge of the results of the reference standard?**  Yes

**Could the conduct or interpretation of the index test have introduced bias?**  Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**  Low concern

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**  2 years follow up.

**Is the reference standard likely to correctly classify the target condition?**  Yes

**Were the reference standard results interpreted without knowledge of the results of the index tests?**  No

**Could the reference standard, its conduct, or its interpretation have introduced bias?**  Low risk

#### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**  Low concern

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**  All patients appear to be accounted for

**Was there an appropriate interval between index test and reference standard?**  Yes

**Did all patients receive the same reference standard?**  Yes

**Were all patients included in the analysis?**  Yes

**Could the patient flow have introduced bias?**  Low risk

### NOTES

In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.
### Shephard (2013)

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

| Attempts were made within the design or analysis to balance the comparison groups for potential confounders? | Yes |
| The groups were comparable at baseline, including all major confounding and prognostic factors? | Yes |

**Could the selection of patients have introduced bias?** High risk

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases:</strong></td>
</tr>
<tr>
<td><strong>Controls:</strong></td>
</tr>
</tbody>
</table>

**Inclusion criteria:**

Cases: Patients with a record of one of 22 GPRD kidney cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a kidney cancer code was assigned the data of diagnosis/index date.

Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.

**Exclusion criteria:** Metastatic cancer to the kidney from a non-kidney primary, diagnosis before 2000, or no consultations in the year before diagnosis.

**Clinical setting:** Primary care

| Are there concerns that the included patients and setting do not match the review question? | Low concern |

#### INDEX TEST

**A. Risk of bias**

| Index test | A list of symptoms, signs and investigations (features) potentially associated with kidney cancer was compiled from the authors’ literature search, augmented by viewing material from kidney cancer support organisations and online chat rooms. Internet search terms included ‘kidney cancer’, ‘kidney cancer symptoms’, and ‘early signs/indications kidney cancer’. Visible and non-visible haematuria were studied separately. Only codes specifying the word ‘microscopic’ were assigned to the latter group, so generic codes such as the single word ‘haematuria’ were assumed to be visible haematuria. Over 1800 GPRD codes were compiled for the putative |

---

Suspected Cancer: Appendix F (June 2015)  Page 1022 of 1735
features of kidney cancer from the GPRD’s master list of over 100,000 codes. Occurrences of these features in the year before the index date were identified. Repeated consultations for the same complaint were also identified along with all codes for fractures as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Variables were retained only if they occurred in at least 5% of either cases or controls. Investigation results were deemed to be abnormal if they fell outside their local laboratory’s normal range: for analysis, patients with a normal laboratory result were grouped with those who had not been tested. The raised inflammatory markers variable was a composite of any of abnormal erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein; similarly abnormal liver function tests reflected a raised value of any of the hepatic enzymes reported by each laboratory.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
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<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td>Yes</td>
</tr>
<tr>
<td>Investigators were kept ‘blind’ to other important confounding and prognostic factors?</td>
<td></td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>REFERENCES STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Kidney cancer code in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>A total of 18890 patients were identified, 15707 controls and 3183 cases. Of the controls the following exclusions were applied: bladder cancer (N = 29), metastatic cancer (N = 104), and no data in year pre-index date (N = 1483). Of the cases the following exclusions were applied: No controls (N = 2), metastatic cancer (N = 24), and bladder cancer (N = 8).</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Could the patient flow have introduced bias?  |  Low risk
---|---
**NOTES** | 24 symptoms and 22 abnormal test results were considered initially. 10 symptoms and 11 abnormal test variables were present in ≥ 5% of cases.

## References

### Included studies


### Excluded studies (with excl reason)


Not in PICO


Not in PICO


Not in PICO
Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO
Not in PICO

Not in PICO

Not in PICO/Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO
_Praactitioner_, 250: 4-6.
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Review question:
Which investigations of symptoms of suspected renal cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

<table>
<thead>
<tr>
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<th>No of references retrieved</th>
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<tbody>
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<td>Medline</td>
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<td>Premedline</td>
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<td>Cochrane Library</td>
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<tr>
<td>Psychinfo</td>
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</tr>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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<td>Biomed Central</td>
<td>1980-2013</td>
<td>814</td>
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Total References retrieved (after de-duplication): 189

Update Search

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<td>Premedline</td>
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<td>2/2013-18/08/2014</td>
<td>11</td>
<td>2</td>
<td>18/08/2014</td>
</tr>
</tbody>
</table>

Not in PICO


Study results

No evidence was identified pertaining to the diagnostic accuracy of abdominal ultrasound, urine cytology, x-ray, intravenous pyelogram, or CT scan of the abdomen and pelvis in patients with suspected renal cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review

Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO
Brown, F. M. (2000) Urine cytology. It is still the gold standard for screening?. [Review] [25 refs].  
Narrative review

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Already included

Not in PICO

Not in PICO

Narrative review


Endourology, 26: A94-A95.
Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (Not diagnostic test accuracy study)

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Narrative review

Narrative review

Narrative review

Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


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Narrative review


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Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO/Narrative review


Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO (outcomes not relevant, referred population[7])


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review

Not in PICO


Systematic review, have checked relevance of included papers


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO

Narrative review

Abstract only so limited information, but I think it's not in PICO (referred patients because from Germany and authors from urology department)

Abstract only so limited information, but I think it's not in PICO (referred patients because from Germany and authors from urology department)

Abstract only so limited information, but I think it's not in PICO (referred patients because from Germany and authors from urology department)

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (setting; Willie agrees; also came up in bladder search)

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO (at least 17/27 had cancer)


Narrative review


Not in PICO (at least 17/27 had cancer)


Narrative review


Vasdev, N. & Thorpe, A. C. (2011) Has the introduction of the '2 week rule' in the UK led to an earlier diagnosis of urological malignancy? ecancermedicalscience, 5. Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO (referred population)

Not in PICO

Not in PICO


**TESTICULAR CANCER**

**Review question:**
What is the risk of testicular cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
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<tr>
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Study results

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Excl reason: Not in PICO

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Bleyer, A. CAUTION! Consider Cancer: Common Symptoms and Signs for Early Detection of Cancer in Young Adults. Seminars in Oncology 36[3], 207-212. 2009.
Excl reason: Narrative review

Excl reason: Not in PICO

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Excl reason: Not in PICO
Bridges, B. and Hussain, A. Testicular germ cell tumors. [Review] [45 refs]. Current Opinion in Oncology 18[3], 271-276. 2006. Excl reason: Not in PICO


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Dieckmann, K. P., Kulejewski, M., Pichlmeier, U., and Loy, V. Diagnosis of contralateral testicular intraepithelial neoplasia (TIN) in patients with testicular germ cell cancer: systematic two-site biopsies are more sensitive than a single random biopsy. European Urology 51[1], 175-183. 183. Excl reason: Not in PICO


Docimo, S. G., Silver, R. I., and Cromie, W. The undescended testicle: diagnosis and management. [Review] [34 refs]. American Family Physician 62[9], 2037-2044. 2047. Excl reason: Not in PICO


Foster, P. W., Ritchie, A. W., and Jones, D. J. Prospective analysis of scrotal pathology referrals - are referrals appropriate and accurate? Annals of the Royal College of Surgeons of England 88[4],

Excl reason: Not in PICO


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Surgery 89[1], 82-89. 1985.
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Leyh, H. Case history and palpation are the basis of early diagnosis of testicular tumors. [German]. Medizinische Klinik 79[22], 612-615. 1984.
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Muller, T., Gozzi, C., Akkad, T., Pallwein, L., Bartsch, G., and Steiner, H. Management of incidental impalpable intratesticular masses of < or = 5 mm in diameter. BJU International 98[5], 1001-1004. 2006.
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Noonan, A. M., Carney, D. N., and McCaffrey, J. Study to assess satisfaction of general practitioners (GP) with oncology services, GP awareness of follow-up guidelines for patients with cancer, and GP access to oncology services. Journal of Clinical Oncology 29[15 SUPPL. 1], 20-5-2011.
Excl reason: Not in PICO

Nordhaus, C., Stief, C. G., and Tullmann, E. M. [Inspection, palpation and ultrasound--the basics for clinical examination of the scrotum and testes]. [German]. MMW Fortschritte der Medizin 151[23], 39-40. 4-6-2009.
Excl reason: Narrative review


Oosterlinck, W., Dekuyper, P., Christiaens, T., and De, Maeseneer J. Audit of non-profit referrals of general practitioners to an (academic) urological consultation. [Dutch]. Tijdschrift voor Geneeskunde 62[10], 782-787. 15-5-2006. Excl reason: Not in PICO


Excl reason: Not in PICO

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Raghavan, D. Towards the earlier diagnosis of testicular cancer. [Review] [20 refs]. Australian Family Physician 19[6], 865-875. 1990.
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Shaw, J. Diagnosis and treatment of testicular cancer. [Review] [37 refs]. American Family Physician 77[4], 469-474. 15-2-2008.
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Shokar, Gurjeet S., Carlson, Carol A., Davis, Brian, and Shokar, Navkiran K. Testicular Cancer Screening in a Primary Care Setting. [References]. International Journal of Men's Health 2[3], 221-228. 2003.
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Thorup, J. and Cortes, D. Surgical treatment and follow up on undescended testis. [Review] [50 refs]. Pediatric Endocrinology Reviews 7[1], 38-43. 2009.
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Excl reason: Not in PICO (patients with suspected testicular cancer)

Vasdev, N. and Thorpe, A. C. Has the introduction of the '2 week rule' in the UK led to an earlier diagnosis of urological malignancy? ecancermedicalscience 5[1]. 31-8-2011.
Excl reason: Not in PICO

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Excl reason: Narrative review

Walsh, T. J., Dall’Era, M. A., Croughan, M. S., Carroll, P. R., and Turek, P. J. Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer. [Review] [21 refs]. Journal of Urology 178[4:Pt 1], t-6. 2007.
Excl reason: Not in PICO

Wampler, S. M. and Llanes, M. Common scrotal and testicular problems. [Review]. Primary Care; Clinics in Office Practice 37[3], 613-626. 20-11-2010.
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Wilson, C., Boyd, K., Mohammed, A., and Little, B. A single episode of haematospermia can be safely managed in the community. International Journal of Clinical Practice 64[10], 1436-1439. 2010.
Excl reason: Not in PICO

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**Review question:**
Which investigations of symptoms of suspected testicular cancer should be done with clinical responsibility retained by primary care?

**Results**

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Not in PICO


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Guideline


Not in PICO


Not in PICO


Narrative review


Not in PICO


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on morphologically difficult-to-classify areas. Modern Pathology, 22: 1066-1074.
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Vasdev, N. & Thorpe, A. C. (2011) Has the introduction of the '2 week rule' in the UK led to an earlier diagnosis of urological malignancy? *ecancermedicalscience*, 5.

Not in PICO


Not available, and doesn't appear to be relevant.


Not in PICO


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Not in PICO
PENILE CANCER

Review question:
What is the risk of penile cancer in patients presenting in primary care with symptom(s)?

Results

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Study results

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None

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Kohn, F. M. [Skin changes of the penis. Differentiation between local findings and systemic diseases!]. [German]. MMW Fortschritte der Medizin 144[12], 30-32. 1934.
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Lucky, M. A., Rogers, B., and Parr, N. J. Referrals into a dedicated British penile cancer centre and sources of possible delay. Sexually Transmitted Infections 85[7], 527-530. 2009.
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Published as poster abstract only. Not enough information can be extracted to ascertain relevance, but I think it is not in PICO

Excl reason: Narrative review

Wood, S. A guide to common conditions of the penis. [Review] [0 refs]. Practitioner 244[1614], 764-770. 2000.
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**Review question:**
Which investigations of symptoms of suspected penile cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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Study results

No evidence was identified pertaining to the diagnostic accuracy of tests used in patients with suspected penile cancer where the clinical responsibility was retained by primary care.

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Narrative review


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Narrative review

Vasdev, N. & Thorpe, A. C. (2011) Has the introduction of the '2 week rule' in the UK led to an earlier diagnosis of urological malignancy? *ecancermedicalscience*, 5.

Not in PICO


Narrative review


Narrative review


Narrative review


Published as poster abstract only. Not enough information can be extracted to ascertain relevance, but I think it is not in PICO


Narrative review
### SKIN CANCERS

#### MELANOMA

**Review question:**
What is the risk of melanoma in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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Total References retrieved (after de-duplication): 19
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, (4) the fact that the reference standard did not in all cases match that of the current question, namely histology, and 5) data missing.

Study results
Table 1: Melanoma: Study results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI) Prevalence</th>
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<td>Pigmented lesion</td>
<td>All included</td>
<td>1.4 (0.8-2.3)</td>
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<tr>
<td>Lesion-based analysis</td>
<td></td>
<td>patients</td>
<td>England sample</td>
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<tr>
<td>-----------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Walter (2012)</td>
<td>Suspicious pigmented lesions</td>
<td>All included patients</td>
<td>2.3 (1.6-3.2) 36/1573</td>
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<tr>
<td>Lesion-based analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walter (2013)</td>
<td>7PCL: Suspicious pigmented lesions: Change in size of lesion</td>
<td>All included patients</td>
<td>3.8 (2.5-5.5) 26/693</td>
</tr>
<tr>
<td>Lesion-based analysis</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Walter (2013)</td>
<td>7PCL: Suspicious pigmented lesions: Irregular pigmentation</td>
<td>All included patients</td>
<td>4.4 (3.1-6.3) 31/702</td>
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<tr>
<td>Walter (2013)</td>
<td>7PCL: Suspicious pigmented lesions: Irregular border</td>
<td>All included patients</td>
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<tr>
<td>Lesion-based analysis</td>
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<tr>
<td>Walter (2013)</td>
<td>7PCL: Suspicious pigmented lesions: Inflammation</td>
<td>All included patients</td>
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<tr>
<td>Walter (2013)</td>
<td>7PCL: Suspicious pigmented lesions: Itch or altered sensation</td>
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<td>7PCL: Suspicious pigmented lesions: Lesion larger than other (diameter &gt; 7 mm)</td>
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<tr>
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<td>All included patients</td>
<td>8.2 (5.2-12.5) 20/245</td>
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<td>Lesion-based analysis</td>
<td>Original 7PCL: Score ≥ 5*</td>
<td>All included patients</td>
<td>12.3 (6.1-22.6) 9/73</td>
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<tr>
<td>Walter (2013)</td>
<td>Original 7PCL: Score ≥ 6*</td>
<td>All included patients</td>
<td>10.5 (1.8-34.5) 2/19</td>
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<td>Lesion-based analysis</td>
<td>Weighted 7PCL: Score ≥ 1**</td>
<td>All included patients</td>
<td>2.7 (1.9-3.8) 36/1334</td>
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<tr>
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<td>All included patients</td>
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<tr>
<td>Lesion-based analysis</td>
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</tr>
<tr>
<td>Walter (2013)</td>
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<td>All included patients</td>
<td>4.8 (3.4-6.8) 33/685</td>
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<tr>
<td>Lesion-based analysis</td>
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<td>All included patients</td>
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<tr>
<td>Walter (2013)</td>
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<td>All included patients</td>
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<td>Lesion-based analysis</td>
<td>Weighted 7PCL: Score ≥ 7**</td>
<td>All included patients</td>
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<tr>
<td>Walter (2013)</td>
<td>Weighted 7PCL: Score ≥ 8**</td>
<td>All included patients</td>
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<tr>
<td>Lesion-based analysis</td>
<td>Weighted 7PCL: Score ≥ 9**</td>
<td>All included patients</td>
<td>8.3 (0.4-40.2) 1/12</td>
</tr>
</tbody>
</table>

* Original 7PCL consists of 7 items (change in shape, size and/or colour, inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) and each present feature score 1 point. ** The Weighted 7PCL consists of the same 7 items, but these are divided into major (change in
shape, size and/or colour) scoring 2 points each and minor (inflammation, crusting/bleeding, sensory change, diameter ≥ 7 mm) scoring 1 point.

Evidence statement(s):

Pigmented skin lesions presenting in a primary care setting are associated with positive predictive values of 0.8-5.1% for melanoma (2 studies, N = 2784 lesions), and the positive predictive values increased proportionally to the number of different risk features the lesions displayed up to 15.7% (1 study, 1436 lesions). The studies were associated with 4 bias/applicability concerns (see also Table 1).

Evidence tables

Emery (2010)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
<th>Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin cancer clinics operated by GPs from a metropolitan area)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td></td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). Australia: N = 469 patients, mean age = 50 years, 48% females, with interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma).</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>England: Patients aged &gt; 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged &gt; 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination</td>
<td></td>
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<tr>
<td>Exclusion criteria:</td>
<td>None reported.</td>
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<tr>
<td>Clinical setting:</td>
<td>Primary care, UK, and primary care skin cancer practice, Queensland Australia.</td>
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<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
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</table>
### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.</th>
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<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images</th>
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<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
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<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results</th>
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<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
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<tr>
<td>Were all patients included in the analysis?</td>
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<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
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### NOTES

Analysis was on a per-lesion basis rather than a per-patient basis

---

**Walter (2012; 2013)**

### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective series of suspicious pigmented lesions</th>
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<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
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</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td><strong>Unclear</strong></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Unclear risk</strong></td>
</tr>
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#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas.</th>
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<tr>
<td>Inclusion criteria: Patients aged ≥ 18 years presenting to one of the 15...</td>
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</table>
participating general practices with a suspicious (any lesion presented by a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010.

Clinical setting: UK primary care.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
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</thead>
</table>

### INDEX TEST

**A. Risk of bias**

<table>
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<th>Index test</th>
<th>Suspicious (any lesion presented by a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion</th>
</tr>
</thead>
</table>

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

Could the conduct or interpretation of the index test have introduced bias? | Low risk |

### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

**A. Risk of bias**

<table>
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<tr>
<th>Reference standard(s)</th>
<th>Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.</th>
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</table>

Is the reference standard likely to correctly classify the target condition? | Unclear |

Were the reference standard results interpreted without knowledge of the results of the index tests? | No |

Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk |

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

### FLOW AND TIMING

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results</th>
</tr>
</thead>
</table>

Was there an appropriate interval between index test and reference standard? | Yes |

Did all patients receive the same reference standard? | Yes |

Were all patients included in the analysis? | Yes: Tests: No signs & symptoms (S&S); S&S: Unclear risk |

Could the patient flow have introduced bias? | Tests: Low risk; S&S: Unclear risk |

### NOTES

Data from this study published in 2 papers: Details above refer to the data from Walter (2012). Further publication-specific details for Walter (2013): Of the 1573 included lesions, 42 did not have a reference standard assessment and the 7PCL was not fully completed for a further 95 lesions. The analyses were therefore based on 1436 lesions from 1182 patients (mean age (SD) = 44.7 (16.6) years; 424 males / 758 females with 36 melanomas). Analysis was
on a per-lesion basis rather than a per-patient basis for both papers.

References

Included Studies


Excluded Studies


Not in PICO

Not in PICO

In Russian. Not enough information can be extracted to definitely ascertain whether it is in PICO, but I don't think so.

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO (no symptoms)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

S&S: Population not in PICO; tests: Not a DTA study

Not in PICO (excised lesions only)

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review
Not in PICO (only excised lesions, not examined lesions; no information about symptoms/lesion features)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Letter

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Results only reported in 'number of contacts' for true positives, so PPV cannot be calculated.

Not in PICO
Not in PICO

Narrative review

Narrative review

Not in PICO (only excised lesions, not examined lesions; no information about symptoms/lesion features)

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Guideline


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Same data as Walter 2012


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Same data as Walter (2012) already included.


Not in PICO (for signs and symptoms or for tests)


Not in PICO


Not in PICO


Not in PICO: Data only reported for 3231[excised]/8790[examined] patients.


Not in PICO

**Review question:**

Which investigations of symptoms of suspected melanoma should be done with clinical responsibility retained by primary care?
Results

Literature search

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Total number of studies identified after de-duplication: 300

Update Search

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<td>19/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>2013-19/08/2014</td>
<td>70</td>
<td>20</td>
<td>19/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 42

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study populations may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the criteria for malignancy of the index test are not specified in one case which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole in some cases and not for melanoma separately. The reference standards employed were also subject to high or unclear risk of bias in the majority of the studies.

### Study results

#### Table 1: Melanoma: SIAscan/MoleMate

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Prevalence</th>
<th>Sensitivity  % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Positive predictive value % (95% CI)</th>
<th>False negativity rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emery (2010)</td>
<td>SIAscan/MoleMate: Moncrieff scoring system</td>
<td>England development set: 24 “suspicious” and 3 melanomas /422 lesions</td>
<td>54 (35-72)</td>
<td>77 (73-81)</td>
<td>12 (7.5-20)</td>
<td>46</td>
</tr>
<tr>
<td>Emery (2010)</td>
<td>SIAscan/MoleMate: Primary scare scoring algorithm</td>
<td>England validation set: 6 “suspicious” and 2 melanomas /208 lesions</td>
<td>50 (18-81)</td>
<td>84 (78-88)</td>
<td>9 (3-22)</td>
<td>50</td>
</tr>
<tr>
<td>Emery (2010)</td>
<td>SIAscan/MoleMate: Primary scare scoring algorithm</td>
<td>Australia dataset: 45 “suspicious” and 11 melanomas /581 lesions</td>
<td>44 (32-58)</td>
<td>95 (93-97)</td>
<td>52 (38-66)</td>
<td>56</td>
</tr>
</tbody>
</table>
Evidence statement(s):

SIAscan/MoleMate (2 studies, N = 1977 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 44-100%, specificities ranging between 71.79-95%, positive predictive values ranging between 7.86-52%, and false negativity rates ranging between 0-56% for skin cancer/ melanoma. The studies were each associated with 3-4 bias/applicability concerns (see also Table 1).

Dermatoscopy/dermoscopy with and without clinical images or sequential digital dermoscopy imaging (2 studies, N = 794 lesions) performed in symptomatic patients presenting in a primary care setting is associated with sensitivities ranging between 53.1- 82.6%, specificities ranging between 80-92.8%, positive predictive values ranging between 34-44.4%, and false negativity rates ranging between 17.4-46.9% for skin cancer/ melanoma. The studies were each associated with 3 bias/applicability concerns (see also Table 2).

Evidence tables

Emery (2010)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Prevalence</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Positive predictive value % (95% CI)</th>
<th>False negativity rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menzies (2009)</td>
<td>Dermoscopy</td>
<td>Unclear/331 lesions</td>
<td>53.1 (34.7-70.9)</td>
<td>89 (84.9-92.3)</td>
<td>34 (21.2-48.8)</td>
<td>46.9</td>
</tr>
<tr>
<td>Menzies (2009)</td>
<td>Dermoscopy ± sequential digital dermoscopy imaging</td>
<td>Unclear/331 lesions</td>
<td>71.9 (53.3-86.3)</td>
<td>86.6 (82.2-90.3)</td>
<td>36.4 (24.7-49.6)</td>
<td>28.1</td>
</tr>
<tr>
<td>Menzies (2009)</td>
<td>Sequential digital dermoscopy imaging</td>
<td>Unclear/149 lesions</td>
<td>72.7 (39-94)</td>
<td>92.8 (87.1-96.5)</td>
<td>44.4 (21.5-69.2)</td>
<td>27.3</td>
</tr>
<tr>
<td>Rosendahl (2011)</td>
<td>Clinical images and dermatoscopy</td>
<td>138 malignacies/463 lesions</td>
<td>82.6</td>
<td>80</td>
<td>Not reported</td>
<td>17.4</td>
</tr>
</tbody>
</table>

There was no evidence relating to the diagnostic accuracy of biopsy or ophthalmoscopy for diagnosing melanoma in a primary care setting.
Was a consecutive or random sample of patients enrolled? | Unclear
---|---
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Unclear risk

**B. Concerns regarding applicability**

| Patient characteristics and setting | England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). For the evaluation of SIAscopy this sample was further split into 2 samples: Development: N = 422 lesions of which 0 were squamous cell carcinoma, 0 were basal cell carcinoma, 3 were melanoma and 0 were lentigo maligna. Validation: N = 208 lesions of which 0 were squamous cell carcinoma, 0 were basal cell carcinoma, 2 were melanoma and 0 were lentigo maligna. Australia: N = 469 patients, mean age = 50 years, 48% females, with interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma). |

Inclusion criteria:
England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006. Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination

Exclusion criteria: None reported.
Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.

Are there concerns that the included patients and setting do not match the review question? | Unclear concern

**INDEX TEST**

**A. Risk of bias**

| Index test | Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.
SIAscan images and data (including the location of the lesion and the age group and sex of the patients) were assessed by a SIAscopy expert, who was blinded to the 7-point melanoma checklist results and clinical photographs. The SIAscopy expert scored the presence or absence of each specific SIAscopic feature including those previously associated with melanoma (Moncrieff et al. (2002) Br J Dermatol, 146: 448-57): Size of lesion, age of patient, dermal melanin, collagen holes and blood displacement with erythematous blush. Additional features that were also scored were blood vessels, white dots on the collagen view, blood lacunes and a cerebriform melanin pattern.
From this information a primary care scoring algorithm was developed: |
All lesions -> Any collagen white dots OR cerebriform pattern?  
Yes -> Seborrhoeic keratosis STOP  
No -> Any blood lacunes?  
Yes - > Haemangioma STOP  
No - >  
Dermal melanin within the lesion: 3 points  
Presence of any blood vessels: 2 points  
Blood displacement with erythematous blush: 1 point  
Maximum diameter > 6 mm: 1 point  
For every COMPLETED 15 years of age: 1 point  
Score of 6 or more?  
Yes -> Suspicious  
No-> Not suspicious

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes           |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk     |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

| Reference standard(s) | Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images |

| Is the reference standard likely to correctly classify the target condition? | Unclear |

| Were the reference standard results interpreted without knowledge of the results of the index tests? | Yes       |

| Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

**FLOW AND TIMING**

**A. risk of bias**

| Flow and timing | All patients are accounted for in the results |

| Was there an appropriate interval between index test and reference standard? | Yes |

| Did all patients receive the same reference standard? | Yes |

| Were all patients included in the analysis? | Yes |

| Could the patient flow have introduced bias? | Low risk |

**NOTES**

Analysis was on a per-lesion basis rather than a per-patient basis. Please note the diagnostic accuracy results given above relates to the diagnosis of a “suspicious” lesion, and not just melanomas. The 2-by-2 tables could not be extracted.

**Menzies (2009)**

**PATIENT SELECTION**

**A. risk of bias**
### Patient sampling

| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| Could the selection of patients have introduced bias? | Low risk |

### Patient characteristics and setting

102 GPs were initially recruited, 74 of whom completed the educational intervention and online assessment of learning. 63 GPs from 19 practices assessed 374 lesions as requiring referral or excision (median number of lesions per GP = 6, mean = 5.9, SD = 3). No other information reported.

**Inclusion criteria:**
Consecutive patients with pigmented lesions (some brown, grey, blue or black colour within some part of the lesion) which, after routine naked eye examination by the GP would have been biopsied or referred (that is, a suspicious pigmented lesion) presenting to GPs who worked in practices in metropolitan Perth with a minimum of 3 doctors. The GPS and practices had to meet the following criteria: A history of excision or referral of at least 10 pigmented skin lesions over the previous 12-month period for each doctor, and available space for a sequential digital dermoscopy imaging device. During the pretrial period all GPs underwent a training program in the use of dermoscopy and sequential digital dermoscopy imaging. This included reading a textbook in dermoscopic diagnosis and the use of sequential digital dermoscopy imaging, and a tutorial on a CD-rom showing examples of changed and unchanged monitored lesions. In addition, GPs attended a 2 hour workshop on the use of diagnostic devices and recruitment procedures. The training was assessed through an online pre- and post-education intervention test of 245 lesions not seen in the textbook or on the CD-rom. Answers were provided during the post-test as a component of the educational intervention. Before formal patient recruitment began, GPs assessed at least one pretrial lesion to determine the quality of imaging with the sequential digital dermoscopy imaging device and undertake completion of the trial paperwork. GPs were allowed to practise using the dermoscopy device during this pretrial phase. The pretrial phase of education and run-in period occurred from May 2005 to January 2006.

**Exclusion criteria:** GPs who already used dermoscopy or sequential digital dermoscopy imaging in their routine practice.

**Clinical setting:** Primary care, Australia.

### Are there concerns that the included patients and setting do not match the review question?

| Unclear concern |

### INDEX TEST

#### A. Risk of bias

**Index test**

Dermoscopy examination performed using a hand-held oil immersion glass plate device (Delta 10 Dermatoscope: Heine Ltd, Herrsching, Germany). All lesions were then photographed with the dermoscopy imaging device (Sentry pilot; Polartechnics Ltd, Sydney, Australia). This incorporated a higher resolution megapixel camera which could be used for telemedicine diagnosis and for colour-calibrated sequential digital dermoscopy imaging. For melanocytic lesions that did not have dermoscopic evidence of melanoma, but were still considered to be suspicious, short term sequential digital dermoscopy imaging was performed over a period of 3 months.
<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Hierarchical diagnosis order of (1) histopathology, (2) unchanged lesions after sequential digital dermoscopy imaging indicating a benign diagnosis, (3) specialist opinion following referral, and (4) dermoscopy telemedicine. All sequential digital dermoscopy imaging and dermoscopy telemedicine images of nonexcised lesions were reviewed by an expert in dermoscopy and sequential digital dermoscopy imaging and a diagnosis recorded.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>The results only appear to be reported for 348/374 lesions for dermoscopy and dermoscopy ± sequential digital dermoscopy imaging (for melanoma: of which 9 had an unknown diagnosis and 8 had a diagnosis of basal cell carcinoma or Bowen disease – these were all excluded from the analyses) and for 160/192 lesions that received sequential digital dermoscopy imaging (for melanoma: of which 9 had an unknown diagnosis and 2 had a diagnosis of basal cell carcinoma or Bowen disease – these were all excluded from the analyses).</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear, but probably</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>No</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>High risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Analysis appears to be on a per-lesion basis rather than a per-patient basis. The 2-by-2 tables could not be extracted.</td>
</tr>
<tr>
<td>Rosendahl (2011)</td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Probably</td>
</tr>
</tbody>
</table>
Could the selection of patients have introduced bias?  | Low risk
---|---

B. Concerns regarding applicability

**Patient characteristics and setting**

N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin.

Final diagnoses:

- Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7.

Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. *Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection.*

Exclusion criteria: Poor image quality (N = 3).

Clinical setting: Primary care skin cancer practice in Queensland, Australia

Are there concerns that the included patients and setting do not match the review question? | Unclear concern
---|---

INDEX TEST

A. Risk of bias

**Index test**

For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatoscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, CA); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH, Herrsching, Germany) were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour ("chaos") and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods, polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.*

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes
<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Unclear risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Histopathology</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td></td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignacies</td>
</tr>
</tbody>
</table>

**Walter (2012)**

**PATIENT SELECTION**

| **A. risk of bias** |  |
| Patient sampling | Prospective series of suspicious pigmented lesions |
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Unclear |
| **Could the selection of patients have introduced bias?** | Unclear risk |

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 643 patients, mean age (SD) = 44.5 (16.7) years; 230 males / 413 females with N = 788 lesions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented by a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Patients who were unable to give informed consent or were considered inappropriate to include by their family doctor.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>UK primary care.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>Clinical assessment (clinical history and naked eye examination) followed by SIAscopy/MoleMate system (assessing clinician had completed a 2-hour training CD-ROM to identify relevant SIAscopic features of various pigmented skin lesions).</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reference standard(s)</strong></td>
<td>Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>Data are missing for 22/788 lesions</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes Tests: No</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td>Analysis was on a per-lesion basis rather than a per-patient basis. TP = 18, FN = 0, FP = 211, TN = 537.</td>
</tr>
</tbody>
</table>

**Cost-effectiveness evidence**

**Information sources and eligibility criteria**

The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED and HEED. Studies conducted in OECD countries other than the UK were considered.
Studies were selected for inclusion in the evidence review if the following criteria were met:

- Both cost and health consequences of interventions reported (i.e. true cost-effectiveness analyses)
- Conducted in an OECD country
- Incremental results are reported or enough information is presented to allow incremental results to be derived
- Studies that matched the population, interventions, comparators and outcomes specified in PICO
- Studies that meet the applicability and quality criteria set out by NICE, including relevance to the NICE reference case and UK NHS

Note that studies that measured effectiveness using quality of life based outcomes (e.g. QALYs) were desirable but, where this evidence was unavailable, studies using alternative effectiveness measures (e.g. life years) were considered.

Selection of studies

The literature search results were screened by checking the article’s title and abstract for relevance to the review question. The full articles of non-excluded studies were then attained for appraisal and compared against the inclusion criteria specified above.

Results

The diagram below summarises the search and sifting process for this topic.
It can be seen that, in total, 473 possibly relevant papers were identified. Of these, 471 papers were excluded at the initial sifting stage based on the title and abstract while two full papers were obtained for appraisal. One of these papers was excluded based on the full text as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore, only one paper was included in the systematic review of the economic evidence for this topic; Wilson et al. 2012. Mowatt et al. 2010 was a comprehensive report conducted as part of the NIHR HTA programme. The study included was a cost-effectiveness analysis comparing standard care (clinical history, naked eye examination and completion of a seven point checklist) with standard care plus the addition of the Molemate system (SIAscany scanner integrated with a diagnostic algorithm) for the diagnosis of potentially suspicious lesions.

**Quality and applicability of included study**

Wilson et al. 2012 was deemed to be directly applicable to the decision problem that we are evaluating since it considers relevant comparators in the UK primary care setting and takes a NHS and PSS perspective. Results were presented in terms of cost per QALY gained. No serious limitations were identified with the analysis, which was generally of a very high standard.

**Table:** Methodological quality and applicability of the included study

<table>
<thead>
<tr>
<th>Methodological quality</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor limitations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td>Partially applicable</td>
</tr>
<tr>
<td>Wilson et al. 2012</td>
<td></td>
</tr>
</tbody>
</table>
### Modified GRADE table

The primary results of the analysis by Wilson et al. 2012 are summarised in the modified GRADE table below.

<table>
<thead>
<tr>
<th>Methodological quality</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially serious limitations</td>
<td></td>
</tr>
<tr>
<td>Very serious limitations</td>
<td></td>
</tr>
</tbody>
</table>

**Suspected Cancer: Appendix F (June 2015)**
Modified GRADE table showing the included evidence (Wilson et al. 2012) on the cost-effectiveness of adding the molemate system to standard care in patients presenting in primary care with suspected melanoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparators</th>
<th>Costs</th>
<th>Effects</th>
<th>Incr costs</th>
<th>Incr effects</th>
<th>ICER</th>
<th>Uncertainty</th>
<th>Applicability and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al. 2012</td>
<td>Patients presenting in primary care with at least one suspicious pigmented lesion.</td>
<td>Standard Care: Lesions assessed by lead clinician following NICE guidelines including clinical history, naked eye examination and completion of 7 point checklist.</td>
<td>£1115</td>
<td>15.098 QALYs</td>
<td>Reference</td>
<td></td>
<td></td>
<td>Threshold Sensitivity Analysis</td>
<td>Directly Applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The maximum cost per Molemate scan which would result in an ICER less than £30,000 was found to be £290 per consultation.</td>
<td>Analysis conducted from a UK Health Service perspective.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deterministic Sensitivity Analysis</td>
<td>Results reported as incremental cost per QALY.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Use of East of England cancer registry data rather than trial data resulted in an ICER of £3,172 per QALY</td>
<td>Minor Limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Probabilistic Sensitivity Analysis</td>
<td>Further one-way sensitivity analysis could have been conducted.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£18</td>
<td>0.01 QALYs</td>
<td>£1896 per QALY</td>
<td>66.1% of iterations led to an ICER below £30,000 per QALY. The molemate system was dominant in 19.6% and dominated in 7.9% of iterations.</td>
<td></td>
</tr>
</tbody>
</table>

Comments:
**Evidence statement**

Wilson et al (2012) compared the cost-effectiveness of the Molemate system (SIAscopy scanner integrated with a diagnostic algorithm) in addition to usual care (clinical history, naked eye examination and completion of a seven point checklist) in comparison to usual care alone for the diagnosis of potentially suspicious lesions. The authors found that the addition of the Molemate system would increase lifetime costs by £18 and yield an additional 0.01 QALYs per patient. The resulting ICER of £1,896 per QALY falls well below the NICE threshold of £20,000 per QALY and so the base case results suggest that Molemate is a cost-effective addition to usual care.

The addition of the Molemate scan also appears to be cost-effective in an alternative analysis in which East of England cancer registry data were used rather than the trial data with an ICER of £3,172 per QALY. Furthermore, a threshold analysis showed that the cost of adding the Molemate scan would have to exceed £290 for it to no longer be considered cost-effective at a threshold of £30,000 per QALY. The true cost of adding the Molemate scan is unlikely to be as high as this and so this too appears to be a strong result.

The probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the addition of the Molemate scan was cost-effective in 60.3% of iterations. This suggests that there is considerable uncertainty, which the authors attribute to uncertainty in the sensitivity and specificity of Molemate versus usual care and the risk of disease progression in undiagnosed melanoma.

While these results appear favourable, further consideration needs to be given to the key effects that are driving the result. The results were primarily driven by the differences in diagnostic accuracy between the two strategies, which were informed by RCT evidence showing that Molemate had higher sensitivity and lower specificity than usual care. However, only the lower specificity result was found to be statistically significant. Indeed, the conclusion drawn from the trial was that Molemate did not add to best application of NICE guidelines in terms of appropriateness of referral.

Furthermore, the implications of the diagnostic accuracy data used in the model is that both appropriate and inappropriate referrals would be increased by using the Molemate system (driven by better sensitivity and poorer specificity, respectively). Therefore, the results of the model essentially suggest that benefits of picking up more cancer through appropriate referral outweigh the costs of making more inappropriate referrals. In other words, a policy of ‘over-referring’ may be cost-effective.

This interpretation has implications for the cost-effectiveness of the Molemate system itself as it could be argued that the Molemate system is not actually required to achieve such a policy. Being less strict as primary care gatekeepers would very likely lead to similarly cost-effective outcomes without the need for the additional spending on the Molemate system. Indeed, it could be further argued that it would be counter-intuitive to spend money on a system that has only been proven to decrease specificity in comparison to current best practice.
References

Included Studies


Excluded Studies

Narrative review

Not in PICO


Narrative review

Not in PICO


Narrative review

Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO (reference standard is expert opinion, not follow up and histopathology)

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO (secondary care)

Not in PICO

Not in PICO

Guideline

Guideline

Narrative review

Not in PICO

Not in PICO

Not in PICO

Dermatologia, 86: 215-221.

Not in PICO

Narrative review

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Duplicate

Not in PICO


Not in PICO


Not in PICO (secondary care)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO
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Narrative review

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Not in PICO


Not in PICO (secondary care)


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Not in PICO


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Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Letter


Not in PICO


Narrative review


Not in PICO
Narrative review

Narrative review

Not in PICO

LeBoit, P. E. (2009) What sentinel node biopsy in patients with melanoma (or patients whose doctors worry that they could have melanoma) might and might not do. [Review] [12 refs]. Clinics in Dermatology, 27: 588-593.
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

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Narrative review

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Narrative review

Narrative review

Guideline

Not in PICO (secondary care)

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO (secondary care)

Narrative review

Narrative review

Letter

Not in PICO

Narrative review

Menzies, S. W., Moloney, F. J., Byth, K., Avramidis, M., Argenziano, G., Zalaudek, I., Braun, R. P., Malvehy, J., Puig, S., Rabinovitz, H. S., Oliviero, M., Cabo, H., Bono, R., Pizzichetta, M. A., Claeson,

Not in PICO


Narrative review


Not in PICO


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Narrative review


Narrative review


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Letter

Duplicate

Not in PICO

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Narrative review

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Guideline

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Narrative review

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Narrative review


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Guideline


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Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Systematic review, no new studies identified. Relevant studies will be include separately.

Narrative review

Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Protocol


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO
Not in PICO
Wolf, O. & Shalom, A. (1111) [Dermoscopy--a glimpse into the skin]. [Review] [Hebrew]. Harefuah, 149: 519-523.
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
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Not in PICO
Not in PICO
Not in PICO

Not in PICO

SQUAMOUS CELL CARCINOMA

Review question:
What is the risk of squamous cell carcinoma in patients presenting in primary care with symptom(s)?

Results

Literature search

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
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<tbody>
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<td>Medline</td>
<td>All-2012</td>
<td>501</td>
<td>66</td>
<td>09/01/2013</td>
</tr>
<tr>
<td>Premedline</td>
<td>All-2012</td>
<td>66</td>
<td>5</td>
<td>09/01/2013</td>
</tr>
<tr>
<td>Embase</td>
<td>All-2012</td>
<td>2129</td>
<td>76</td>
<td>15/01/2013</td>
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<tr>
<td>Cochrane Library</td>
<td>All-2012</td>
<td>201</td>
<td>3</td>
<td>16/01/2013</td>
</tr>
<tr>
<td>Psychinfo</td>
<td>All-2012</td>
<td>4</td>
<td>1</td>
<td>09/01/2013</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>All-2012</td>
<td>569</td>
<td>36</td>
<td>16/01/2013</td>
</tr>
<tr>
<td>Biomed Central</td>
<td>All-2012</td>
<td>287</td>
<td>3</td>
<td>21/01/2013</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 151

Update Search

<table>
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<th>Database name</th>
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</tr>
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<tr>
<td>Cochrane Library</td>
<td>2013-11/08/2014</td>
<td>48</td>
<td>0</td>
<td>11/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>2013-11/08/2014</td>
<td>89</td>
<td>7</td>
<td>11/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 20
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.

Study results
Table 1: Squamous cell carcinoma of the skin: Study results.
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI) Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emery (2010) Patient-based analysis</td>
<td>Pigmented lesion</td>
<td>All included patients</td>
<td>0 (0-0.6) 0/858</td>
</tr>
<tr>
<td></td>
<td></td>
<td>England sample</td>
<td>0 (0-1.2) 0/389</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Australia sample</td>
<td>0 (0-1) 0/469</td>
</tr>
<tr>
<td>Walter (2012) Lesion, not patient-based analysis</td>
<td>Suspicious pigmented lesions</td>
<td>All included patients</td>
<td>0.06 (0.003-0.4) 1/1573</td>
</tr>
<tr>
<td>Rosendahl (2012) Lesion, not patient-based analysis</td>
<td>Non-pigmented raised skin lesions</td>
<td>All included patients</td>
<td>SCC total: 41.26 (34.5-48.3) 85/206</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCC: 15.53 (11-21.4) 32/206</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Keratoacanthoma: 14.08 (9.8-19.8) 29/206</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bowen disease: 11.65 (7.8-17) 24/206</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>SCC and KA: 31.81 (21.2-44.6) 21/66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>SCC and KA: 28.57 (21.4-36.9) 40/140</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions on head and neck</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 23.33 (15.3-33.7) 21/90</td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions on trunk</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 14.29 (6.4-27.9) 7/49</td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions on upper extremities</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 45.16 (27.8-63.7) 14/31</td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions on lower extremities</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 52.78 (35.7-69.2) 19/36</td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions with monomorphic vascular pattern</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 26.47 (19.5-34.8) 36/136</td>
</tr>
<tr>
<td></td>
<td>Non-pigmented raised skin lesions with polymorphic vascular</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 31.71 (18.6-48.2) 13/41</td>
</tr>
<tr>
<td>pattern</td>
<td>Patients with specific symptom</td>
<td>SCC and KA</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel absent</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 39.29 (22.1-59.3) 11/28</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel morphologic findings: Dots</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 0 (0-95) 0/1</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel morphologic findings: Coils</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 40 (30.1-49.8) 44/110</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel morphologic findings: Serpentine</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 9.76 (4.6-18.8) 8/82</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel morphologic findings: Looped</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 41.67 (22.8-63.1) 10/24</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: No arrangement</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 36.7 (27.8-46.5) 40/109</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: Radial</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 41.18 (19.4-66.5) 7/17</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: Centered</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 0 (0-30.1) 0/12</td>
<td></td>
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<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: Branched</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 0 (0-12.3) 0/35</td>
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<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: Branched and radial</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 2/2 (TP = 2, FP = 0)</td>
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<tr>
<td>Non-pigmented raised skin lesions with vessel arrangement: Others</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 100 (19.8-100) 0/2</td>
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<tr>
<td>Non-pigmented raised skin lesions and keratin</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 52.17 (41.6-62.6) 48/92</td>
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</tr>
<tr>
<td>Non-pigmented raised skin lesions and ulceration</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 27.27 (13.9-45.8) 9/33</td>
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</tr>
<tr>
<td>Non-pigmented raised skin lesions with white structures: White clods</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 20 (5.3-48.6) 3/15</td>
<td></td>
</tr>
<tr>
<td>Non-pigmented raised skin lesions with white</td>
<td>Patients with specific symptom</td>
<td>SCC and KA: 47.06 (3.2-61.4)</td>
<td></td>
</tr>
</tbody>
</table>
Suspected Cancer: Appendix F (June 2015)

Evidence statement(s):

Pigmented skin lesions (2 studies, N = 2784 lesions) presenting in a primary care setting do not seem to confer a risk of squamous cell carcinoma (1 case observed in total). The studies were associated with 3-4 bias and applicability concerns (See also Table 1).

Non-pigmented raised skin lesions (1 study, N = 206 lesions) presenting in a primary care setting are associated with a positive predictive value of 41.26% for squamous cell carcinoma. The study was associated with 2 bias and applicability concerns (See also Table 1).

Evidence tables

Emery (2010)

PATIENT SELECTION

A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective series of pigmented lesions recruited from England (6 general practices covering urban, suburban and rural areas with a registered population of 52913) and Australia (3 primary care skin cancer clinics operated by GPs from a metropolitan area)</th>
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</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

| Patient characteristics and setting | England: N = 389 patients, mean age = 44.9 years, 68.6% females with, interpretable images from N = 630 lesions. 0/630 lesions were squamous cell carcinoma, 0/630 lesions were basal cell carcinoma, 5/630 lesions were melanoma, and 0/630 lesions were lentigo maligna (melanoma). Australia: N = 469 patients, mean age = 50 years, 48% females, with |

KA = keratoacanthoma; TP = true positives; FP = false positives
interpretable images from N = 581 lesions. 0/581 lesions were squamous cell carcinoma, 22/581 lesions were basal cell carcinoma, 7/581 lesions were melanoma, and 4/581 lesions were lentigo maligna (melanoma).

Inclusion criteria:
England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006.
Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination
Exclusion criteria: None reported.
Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
</table>

**INDEX TEST**  
**A. Risk of bias**

**Index test**  
Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**  
**A. Risk of bias**

**Reference standard(s)**  
Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

|Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

**FLOW AND TIMING**  
**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Could the patient flow have introduced bias?**

Low risk

**NOTES**

**Rosendahl (2012)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective unselected consecutive series of raised non-pigmented lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

N = 186 patients, mean (SD) age = 65 (13) years, 32.8% females with N = 206 lesions. 32/206 lesions were squamous cell carcinoma (SCC), 29/206 lesions were keratoacanthoma (SCC), 24/206 lesions were Bowen disease (SCC), and 56/206 lesions were basal cell carcinoma.

**Inclusion criteria:** Patients presenting with non-pigmented raised lesions treated from March 1 through December 31 2011. All the lesions were excised or biopsied. It is unclear if there were any patients presenting with non-pigmented raised lesions not biopsied/excised who were not included.

**Exclusion criteria:** None reported.

**Clinical setting:** Private primary care skin cancer practice, Queensland Australia.

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Non-pigmented raised skin lesions (not further defined, but see subgroup analyses) evaluated using dermoscopic images</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is the reference standard likely to correctly classify the target condition?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Are there concerns that the target condition as defined**

Low concern
### Flow and Timing

<table>
<thead>
<tr>
<th>A. Risk of Bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients are accounted for in the results</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Notes

Analysis was on a per-lesion basis rather than a per-patient basis; some patients may have had more than one lesion diagnosed as skin cancer though it is not possible to ascertain the actual numbers from the data provided.

---

### Patient Selection

#### A. Risk of Bias

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective series of suspicious pigmented lesions</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas.</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Patients who were unable to give informed consent or were considered inappropriate to include by their family doctor.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>UK primary care.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

---

### Index Test

#### A. Risk of Bias

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

---

### Reference Standard

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without follow up 3-6 months later.</th>
</tr>
</thead>
</table>

**Is the reference standard likely to correctly classify the target condition?**

**Unclear**

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

**No**

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

**Unclear risk**

### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

**Unclear concern**

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results</th>
</tr>
</thead>
</table>

**Was there an appropriate interval between index test and reference standard?**

**Yes**

**Did all patients receive the same reference standard?**

**Yes**

**Were all patients included in the analysis?**

**Yes Tests: No**

**Could the patient flow have introduced bias?**

**Low risk**

### NOTES

**Analysis was on a per-lesion basis rather than a per-patient basis.**

### References

**Included Studies**


### Excluded Studies


Narrative review


Narrative review


Not in PICO

Narrative review


Narrative review


Not in PICO


Not in PICO (cancer patients from one population, symptomatic patients from another population)


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Protocol


Guidelines


Not in PICO


Not in PICO

Not in PICO


261-279.

Narrative review


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO (only excised lesions, not examined lesions)


Not in PICO


Not in PICO


Not in PICO

Narrative review

Not in PICO (only excised lesions, not examined lesions; no information about symptoms/lesion features)

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO


Lin, Y.-C., Perng, C.-L., Chang, Y.-M., Li, Y.-F., Tsai, Y.-M., Wu, G.-J. & Lin, C.-K. (2013) Coexistent squamous cell carcinoma and adenoid basal carcinoma in the uterine cervix and infection with


Narrative review


Narrative review


Not in PICO


Narrative review

Marghoob, A. A. & Marghoob, A. A. (146) Basal and squamous cell carcinomas. What every primary care physician should know. [Review] [20 refs]. Postgraduate Medicine, 102: 139-146.

Narrative review


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Guideline


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Dermato-Venereologica, 90: 595-601.

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO
Terrill, P. J., Fairbanks, S., Bailey, M., Terrill, P. J., Fairbanks, S. & Bailey, M. (2009) Is there just one lesion? The need for whole body skin examination in patients presenting with non-
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO


Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).

Narrative review

**Review question:**
Which investigations of symptoms of suspected squamous cell carcinoma should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>1980-2013</td>
<td>2206</td>
<td>141</td>
<td>07/02/2013</td>
</tr>
<tr>
<td>Premedline</td>
<td>1980-2013</td>
<td>85</td>
<td>9</td>
<td>07/02/2013</td>
</tr>
</tbody>
</table>
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study population may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the index test does not specify the criteria for malignancy which may limit its external validity, and that the results

# of records identified through database searching: N = 313
# of additional records identified through other sources: N = 0

# of records screened: N = 313
# of records excluded: N = 240

# of full-text articles assessed for eligibility: N = 73
# of full-text articles excluded, with reasons: N = 72 (Narrative review: N = 3; Not in PICOC: N = 69)

# of studies included in qualitative synthesis: N = 1
# of studies included in quantitative synthesis (meta-analysis): N = 0
presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole and not for squamous cell carcinoma separately.

Study results

Table 1: Squamous cell carcinoma of the skin: Study results.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>False negativity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosendahl (2011)</td>
<td>Clinical images and dermatoscopy</td>
<td>138 malignacies/463 lesions</td>
<td>82.6% (NR)</td>
<td>80% (NR)</td>
<td>NR (NR)</td>
<td>17.4% (NR)</td>
</tr>
</tbody>
</table>

NR = Not reported

No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion in patients with suspected squamous cell cancer where the clinical responsibility was retained by primary care.

Evidence statement(s):

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for skin malignancy. The study was associated with 1 bias and 2 applicability concerns (See also Table 1).

Evidence tables

Rosendahl (2011)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Probably</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin. Final diagnoses: Malignant lesions: Basal cell carcinoma: N = 72; squamous cell carcinoma: N = 37; melanoma: N = 29. Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7. |
| Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. *Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection.* Exclusion criteria: Poor image quality (N = 3). |
| Clinical setting: Primary care skin cancer practice in Queensland, Australia |

**Are there concerns that the included patients and setting do not match the review question?** Unclear concern

**INDEX TEST**

**A. Risk of bias**

| Index test | For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatoscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, Ca); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH< Herrsching, Germany)were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour (“chaos“) and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods, polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.* |

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test | Unclear risk |
have introduced bias?

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern

REFERENCE STANDARD

A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histopathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

FLOW AND TIMING

A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignancies

References

Included Studies


Excluded Studies

Abbas Q, Celebi ME, Garcia IF, Rashid M. Lesion border detection in dermoscopy images using dynamic programming. Skin Research and Technology 2011;17(1):91-100.


Squamous Cell Carcinoma Sentinel Node Biopsy: A Systematic Review. Otolaryngology-Head and 
Exclusion Reason: Not in PICO
Aitken JF, Janda M, Elwood M, Youl PH, Ring IT, Lowe JB. Clinical outcomes from skin screening 
clinics within a community-based melanoma screening program. Journal of the American 
Academy of Dermatology 2006;54(1):105-14.
Exclusion Reason: Not in PICO
Alendar F, Drljevic I, Drljevic K, Alendar T. Early detection of melanoma skin cancer. Bosnian Journal of 
Basic Medical Sciences 2009;9(1):77-80.
Exclusion Reason: Not in PICO
Albert MR, Weinstock MA. Keratinocyte carcinoma. [Review] [74 refs]. CA: A Cancer Journal for 
Exclusion Reason: Narrative Review
clinical examination: Assessment of index lesions referred to a skin cancer clinic without a total 
body skin examination would miss one in three melanomas. Acta Dermato-Venereologica, 93: 
2013.
Exclusion Reason: Not in PICO
malignancy in exophytic oral mucosal lesions: myth or fact? Head and neck pathology, 7: 149- 
154.
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
Alsharqi A, Wilson N. Will the introduction of new NICE guidelines change the management of basal 
Exclusion Reason: Narrative Review
cell carcinoma: morphologic variability of global and local features and accuracy of diagnosis. 
Exclusion Reason: Not in PICO
Angit C, Sharpe GR. Regional audit on squamous cell carcinoma excision margin. Journal of the 
American Academy of Dermatology 2011;64(2 SUPPL. 1):AB124.
Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO
Anthony S, Ogden E, Blashard M, Schofield JK. Basal cell carcinomas: Impact of national guidance 
on local specialist dermatology Department is likely to be manageable. British Journal of 
Dermatology 2009;161:64-5.
Exclusion Reason: Not in PICO
Arits AHMM, Schlangen MHJ, Nelemans PJ, Kelleners-Smeets NWJ. Trends in the incidence of basal 
cell carcinoma by histopathological subtype. Journal of the European Academy of Dermatology 
Exclusion Reason: Not in PICO
Arlt A, Luckhaupt H, Hildmann H. Diagnosis of recurrent squamous cell carcinomas with the tumor 
Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO

Baade PD, Youl PH, Janda M, Whiteman DC, Del Mar CB, Aitken JF. Factors associated with the number of lesions excised for each skin cancer: a study of primary care physicians in Queensland, Australia. Archives of Dermatology 2008;144(11):1468-76.

Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Narrative review


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
Exclusion Reason: Narrative Review
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Exclusion Reason: Narrative Review
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Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative review
Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Carli P, Chiarugi A, De Giorgi V. Examination of lesions (including dermoscopy) without contact with the patient is associated with improper management in about 30% of equivocal melanomas. Dermatologic Surgery 2005;31(2):169-72.  
Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: N=2

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Cheng A, Bennett A, Pogrel MA, Schmidt BL. Should tumor depth measured from an incisional biopsy be used to guide the decision to perform an elective neck dissection? Journal of Oral and Maxillofacial Surgery 2012;70(9 SUPPL. 2):e-1.  
Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO
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Exclusion Reason: Not in PICO

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Exclusion Reason: N=3

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Exclusion Reason: Not in PICO


Epstein JB, Scully C. Assessing the patient at risk for oral squamous cell carcinoma. [Review] [87 refs]. Special Care in Dentistry 1997;17(4):120-8.


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Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review
FitzGerald KL, Buttner PG, Donovan SA. Nonpigmented skin lesions - how many are nonmelanoma skin cancer? Australian Family Physician 2006;35(7):555-7.

Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

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Exclusion Reason: Guidelines

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Exclusion Reason: Narrative review

Exclusion Reason: Narrative Review

Exclusion Reason: Guidelines

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Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Hernandez-Martin A, Arias-Palomino D, Barahona E, Hidalgo C, Munoz C, Garcia-Higuera I. [Analysis of surgical treatment for nonmelanoma skin cancer performed by dermatologists in a public hospital: clinical-pathological correlation, use of hospital resources, and waiting list time from...
Exclusion Reason: Not in PICO
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Exclusion Reason: Not in PICO
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Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)
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Exclusion Reason: Not in PICO
Myers M, Gurwood AS. Periocular malignancies and primary eye care. [Review] [22 refs]. Optometry (St.Louis, Mo.) 2001;72(11):705-12.
Exclusion Reason: Narrative Review
Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermoscopy versus histology or follow up)

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Narrative Review

Sandison A. Common head and neck cases in our consultation referrals: diagnostic dilemmas in inverted papilloma. [Review] [13 refs]. Head and neck pathology 2009;3(3):260-2
Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Narrative Review
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Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Stockfleth E. Non melanoma skin cancer - Early excision is still the standard in therapy. [German]. Klinikarzt 2002;31(5):122-5.
Exclusion Reason: Narrative Review

Exclusion Reason: Narrative Review

Stolte M. [The new "Vienna Classification" for epithelial neoplasia of the gastrointestinal tract. Pros or cons?]. [Review] [34 refs] [German]. Pathologe 2001;22(1):4-12.
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Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

TerKonda SP, Perdikis G. Non-melanotic skin tumors of the upper extremity. [Review] [50 refs]. Hand Clinics 104;20(3):293-301.
Exclusion Reason: Narrative Review

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Exclusion Reason: Not in PICO

Wright VC. When to suspect squamous cancer at colposcopy. [Review] [22 refs]. Nurse Practitioner 1959;26(9):50-6.
Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: N=2
**BASAL CELL CARCINOMA**

**Review question:**
What is the risk of basal cell carcinoma in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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<th>No of references retrieved</th>
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<td>66</td>
<td>09/01/2013</td>
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<td><em>Embase</em></td>
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Total References retrieved (after de-duplication): 127

**Update Search**

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</table>

Total References retrieved (after de-duplication): 15
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main bias risks and applicability concerns that the studies are subject to relate to (1) the patient sampling method not clearly being consecutive or random, (2) the extent to which the study setting matches UK primary care, (3) the quality of the reference standard, which may not always reliably diagnose the symptoms, and (4) the fact that the reference standard did not in all cases match that of the current question, namely histology.

Study results
Table 1: Basal cell carcinoma: Study results

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emery (2010)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosendahl (2012)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walter (2012)</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence statement(s):

Pigmented skin lesions (2 studies, N = 2784 lesions) presenting in a primary care setting are associated with positive predictive value of 0.64-1.82\% for basal cell carcinoma. The studies were associated with 3-4 bias and applicability concerns (see also Table 1).

Non-pigmented skin lesions (1 study, N = 206 lesions) presenting in a primary care setting are associated with a positive predictive value of 27.18\% for basal cell carcinoma. The study was associated with 2 bias and applicability concerns (see also Table 1).

Evidence tables

Emery (2010)

<table>
<thead>
<tr>
<th>Patient selection</th>
<th>Pigmented lesion</th>
<th>All included patients</th>
<th>England sample</th>
<th>Australia sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion, not patient-, based analysis</td>
<td>Pigmented lesion</td>
<td>1.82 (1.2-2.8) 22/1211</td>
<td>0/630 (0-0.8)</td>
<td>3.79 (2.4-5.8) 22/581</td>
</tr>
<tr>
<td>Walter (2012)</td>
<td>Suspicious pigmented lesions</td>
<td>All included patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion, not patient-, based analysis</td>
<td>Suspicious pigmented lesions</td>
<td>0.64 (0.3-1.2) 10/1573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosendahl (2010)</td>
<td>Non-pigmented raised lesion</td>
<td>All included patients</td>
<td>27.18 (21.3-33.9) 56/206</td>
<td></td>
</tr>
</tbody>
</table>
England: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between January 2005 and January 2006.

Australia: Patients aged > 18 years were recruited into the study by their GP if they presented with concerns about a pigmented skin lesion between April 2008 and January 2009. Additional lesions were also included when a pigmented skin lesion was identified as potentially suspicious during their clinical examination.

Exclusion criteria: None reported.

Clinical setting: Primary care, UK, and primary care skin cancer practice, Queensland Australia.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

Pigmented skin lesions that concerned patients, which were evaluated using macroscopic clinical photographs, dermoscopic images and SIAscan.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**

Histopathology or in-person clinical review of the lesion by one expert, including the 7-point melanoma checklist and digital dermoscopy or clinical diagnosis made on the basis of the 7-point melanoma checklist, photographic and dermoscopy images.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern |

**FLOW AND TIMING**

**A. Risk of bias**

Flow and timing

All patients are accounted for in the results.

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Analysis was on a per lesion basis rather than a per patient basis.

Rosendahl (2012)
### PATIENT SELECTION

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective unselected consecutive series of raised non-pigmented lesions</th>
</tr>
</thead>
</table>

**Was a consecutive or random sample of patients enrolled?** Yes

**Was a case-control design avoided?** Yes

**Did the study avoid inappropriate exclusions?** Unclear

**Could the selection of patients have introduced bias?** Unclear risk

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 186 patients, mean (SD) age = 65 (13) years, 32.8% females with N = 206 lesions. 32/206 lesions were squamous cell carcinoma (SCC), 29/206 lesions were keratoacanthoma (SCC), 24/206 lesions were Bowen disease (SCC), and 56/206 lesions were basal cell carcinoma.</th>
</tr>
</thead>
</table>

**Inclusion criteria:** Patients presenting with non-pigmented raised lesions treated from March 1 through December 31 2011. All the lesions were excised or biopsied. It is unclear if there were any patients presenting with non-pigmented raised lesions not biopsied/excised who were not included.

**Exclusion criteria:** None reported.

**Clinical setting:** Private primary care skin cancer practice, Queensland Australia.

**Are there concerns that the included patients and setting do not match the review question?** Unclear concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Non-pigmented raised skin lesions (not further defined, but see subgroup analyses) evaluated using dermoscopic images</th>
</tr>
</thead>
</table>

**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes

**Could the conduct or interpretation of the index test have introduced bias?** Low risk

#### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histopathology</th>
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</table>

**Is the reference standard likely to correctly classify the target condition?** Yes

**Were the reference standard results interpreted without knowledge of the results of the index tests?** No

**Could the reference standard, its conduct, or its interpretation have introduced bias?** Low risk

#### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results</th>
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**Suspected Cancer: Appendix F (June 2015) Page 1207 of 1735**
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
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<td>Were all patients included in the analysis?</td>
<td>Yes</td>
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<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**
Analysis was on a per lesion basis rather than a per patient basis; some patients may have had more than one lesion diagnosed as skin cancer though it is not possible to ascertain the actual numbers from the data provided.

---

**PATIENT SELECTION**

**A. Risk of bias**

**Patient sampling**
Prospective series of suspicious pigmented lesions

**Was a consecutive or random sample of patients enrolled?** Unclear

**Was a case-control design avoided?** Yes

**Did the study avoid inappropriate exclusions?** Unclear

**Could the selection of patients have introduced bias?** Unclear risk

**B. Concerns regarding applicability**

**Patient characteristics and setting**
N = 1293 patients, mean age (SD) = 44.6 (16.8) years; 465 males / 828 females with N = 1573 lesions, of which 1 was squamous cell carcinoma, 10 basal cell carcinomas, and 36 melanomas.

**Inclusion criteria:** Patients aged ≥ 18 years presenting to one of the 15 participating general practices with a suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion from March 2008 to May 2010.

**Exclusion criteria:** Patients who were unable to give informed consent or were considere3d inappropriate to include by their family doctor.

**Clinical setting:** UK primary care.

**Are there concerns that the included patients and setting do not match the review question?** Low concern

---

**INDEX TEST**

**A. Risk of bias**

**Index test**
Suspicious (any lesion presented buy a patient, or opportunistically seen by a family doctor or practice nurse, that could not immediately be diagnosed as benign and about which the patient could not be reassured) pigmented lesion

**Were the index test results interpreted without knowledge of the results of the reference standard?** Yes

**Could the conduct or interpretation of the index test have introduced bias?** Low risk

---

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**
Expert opinion by a histologist or dermatologist or review by two other dermatology experts of the recorded clinical history and examination, a digital photograph, and MoleMate images where available with or without...
Suspected Cancer: Appendix F (June 2015)

### Flow and Timing

| A. Risk of Bias | 
| --- | --- |
| Flow and timing | All patients are accounted for in the results |
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes Tests: No |
| Could the patient flow have introduced bias? | Low risk |

### Notes

Analysis was on a per lesion basis rather than a per patient basis.

### References

**Included Studies**


**Excluded Studies**


Reason Single Case

Reason Not relevant to PICO
Aldridge, R. B. F. Do laypersons have intrinsic pattern recognition abilities that could be harnessed to allow the accurate and early diagnosis of skin cancers? British Journal of Dermatology Conference [var.pagings], 949-950. 2010.
Reason Not relevant to PICO

Reason Not in PICO

Reason Not in PICO

Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Not relevant to PICO


Reason Narrative review

Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Not relevant to PICO
Reason Not relevant to PICO

Reason Case report

Bruce, A. J., Brodland, D. G., Bruce, A. J., and Brodland, D. G. Overview of skin cancer detection and prevention for the primary care physician. [Review] [34 refs]. Mayo Clinic Proceedings 75[5], 491-500. 2000. UNITED STATES.  
Reason Narrative Review

Reason Not relevant to PICO

Reason Not in PICO

Reason Narrative review

Carli, P., Chiarugi, A., De, Giorgi, V, Carli, Paolo, Chiarugi, Alessandra, and De Giorgi, Vincenzo. Examination of lesions (including dermoscopy) without contact with the patient is associated with improper management in about 30% of equivocal melanomas. Dermatologic Surgery 31[2], 169-172. 2005. United States.  
Reason Not relevant to PICO

Reason No relevant data

Reason Not relevant to PICO

Reason Narrative Review

Reason Narrative Review

Reason Not in PICO

Reason Narrative review

Reason Not relevant to PICO

Corey, K. An analysis of terminology used by primary care physicians to describe concerning lesions referred to an urgent dermatology clinic. Journal of Investigative Dermatology Conference[var.pagings], May. 2012. Reason Not relevant to PICO


De Stefano, A. Features of biopsy in diagnosis of metatypical basal cell carcinoma (Basosquamous Carcinoma) of head and neck. Otolaryngologia Polska 66[6], 419-423. 2012. Poland. Reason Narrative Review

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Reason Not in PICO (only excised lesions, not examined lesions)

Reason Not in PICO

Reason Population not relevant to PIC

Reason Narrative Review

Reason Narrative Review

Reason Not relevant to PICO

Not relevant to PICO

Reason Narrative review

Hungary.
Reason Narrative Review

Gordon, P. M., Cox, N. H., Paterson, W. D., Lawrence, C. M., Gordon, P. M., Cox, N. H., Paterson, W. D., and Lawrence, C. M. Basal cell carcinoma: are early appointments justifiable? British Journal of Dermatology 142[3], 446-448. 2000. ENGLAND.
Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Single Case

Reason Not relevant to PICO

Reason Narrative review


Reason Narrative review


Reason Not relevant to PICO


Reason Not relevant to PICO


Reason Not relevant to PICO


Reason Narrative Review


Reason Not in PICO (only excised lesions, not examined lesions; no information about symptoms/lesion features)

Hochman, M., Lang, P., Hochman, M., and Lang, P. Skin cancer of the head and neck. [Review] [75 refs]. Medical Clinics of North America 83[1], 261-282. 10-9-0010. UNITED STATES.

Reason Narrative Review


Reason Single Case/Narrative Review


Reason Not relevant to PICO


Reason Not in PICO


Reason Not in PICO


Reason Narrative Review


Reason Not relevant to PICO
Reason Narrative Review
Reason Narrative Review
Reason Narrative review
Reason Not relevant to PICO
Reason Not in PICO (only excised lesions, not examined lesions; no information about symptoms/lesion features)
Reason Narrative Review
Reason Not relevant to PICO
Reason Not in PICO
Reason Single Case
Reason Not in PICO
Reason Single Case
Reason Not relevant to PICO
Lober, C. W., Fenske, N. A., Lober, C. W., and Fenske, N. A. Basal cell, squamous cell, and sebaceous gland carcinomas of the periorbital region. [Review] [54 refs]. Journal of the American
Academy of Dermatology 25[4], 685-690. 1991. UNITED STATES.
Reason Narrative Review


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Reason Narrative Review

Reason Narrative review

Reason Narrative Review

Reason Not in PICO

McGregor, J. C. and McGregor, J. C. Skin cancer referrals--could prioritization be a reasonable approach in the new millennium? Scottish Medical Journal 45[3], 77-78. 2000. SCOTLAND.
Reason Narrative Review

Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Narrative Review

Reason Not relevant to PICO

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<td>Moreno, G. Tran. Prospective study to assess general practitioners' dermatological diagnostic skills in a referral setting. Australasian Journal of Dermatology 48[2], 77-82. 2007. Australia.</td>
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Reason Not relevant to PICO

Reason Not in PICO

Reason Narrative Review

Reason Narrative Review

Reason Not in PICO

Reason Awaiting arrival of paper

Reason Health Economics

Reason Narrative Review

Reason Not relevant to PICO

Reason Not in PICO

Reason Not in PICO

Reason Not in PICO

Reason Not in PICO

Reason Narrative review

Reason Outcomes not relevant to PICO


Reason Narrative Review


Reason Narrative Review


Reason Narrative Review


Reason N=2


Reason Not relevant to PICO


Reason Not in PICO

Tate, B. Checking pigmented skin lesions. Medicine Today 8[3], 38-46. 2007. Australia.

Reason Narrative Review


Reason Population not relevant to PICO


Reason Not in PICO


Reason Outcomes not relevant to PICO


Reason Narrative review


Reason Not in PICO
Reason Narrative Review

Twist, M. Rate of incomplete excision of basal cell carcinomas by General Practitioners with Special Interest. British Journal of Dermatology 161[1], 187. 2009.
Reason Not relevant to PICO

Reason Narrative Review

Reason Single Case

Reason Not in PICO

Reason Not in PICO

Reason Not in PICO

Reason Setting not relevant to PICO

Reason Not relevant to PICO

Reason Not relevant to PICO

Reason Narrative Review

Reason Narrative Review

White, G. M., Zhou, H. C. & Burchette, R. J. (2013) Biopsy followed by immediate curettage and electrodesiccation of suspected basal cell carcinomas at the first visit. JAMA Dermatology,
Reason Not in PICO


Reason Not relevant to PICO


Reason Narrative Review


Reason Not relevant to PICO


Reason Not in PICO


Reason Not in PICO


Reason Not in PICO


Reason Same data as Youl (20067), which is not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).


Reason Not in PICO as results only reported for excised lesions (N = 11116, GPs and skin cancer clinic doctors), not examined lesions (N = 28755, GPs and skin cancer clinic doctors).


Reason Narrative Review


Reason Narrative Review

Review question:

Which investigations of symptoms of suspected basal cell carcinoma should be done with clinical responsibility retained by primary care?

Results
### Literature search

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Total number of studies identified after de-duplication: 290

### Update Search

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Total References retrieved (after de-duplication): 23

# of records identified through database searching: N = 313

# of additional records identified through other sources: N = 0

# of records screened: N = 313

# of records excluded: N = 240

# of full-text articles excluded, with reasons: N = 72 (Narrative review: N = 3; Not in PICCO: N = 69)

# of full-text articles assessed for eligibility: N = 73

# of studies included in qualitative synthesis: N = 1

# of studies included in quantitative synthesis (meta-analysis): N = 0
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are that the study population may not be directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, that the index test does not specify the criteria for malignancy which may limit its external validity, and that the results presented are based on a best case scenario, and are therefore likely to be inflated, and only available for skin malignancy as a whole and not for basal cell carcinoma separately.

<table>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>False negativity rate</th>
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<tbody>
<tr>
<td>Rosendahl (2011)</td>
<td>Clinical images and dermatoscopy</td>
<td>138 malignacies/463 lesions</td>
<td>82.6% (NR)</td>
<td>80% (NR)</td>
<td>NR (NR)</td>
<td>17.4% (NR)</td>
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</tbody>
</table>

NR = not reported

No evidence was identified pertaining to the diagnostic accuracy of excision biopsy of the lesion in patients with suspected basal cell cancer where the clinical responsibility was retained by primary care.

Evidence statement(s):

Dermatoscopy and clinical images (1 study, N = 463 lesions/389 patients) performed in symptomatic patients presenting in a primary care setting is associated with a best-case sensitivity of 82.6%, specificity of 80%, and false negativity rate of 17.4% for basal cell carcinoma. The study was associated with 1 bias and 2 applicability concerns (see also Table 1).

Evidence tables

Rosendahl (2011)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
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### A. Risk of bias

<table>
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<tr>
<th>Patient sampling</th>
<th>Consecutive series of lesions submitted for histology from the primary care skin cancer clinic of one of the authors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Probably</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Patient characteristics and setting | N = 463 pigmented lesions from 389 patients, mean (SD) age = 57 (17) years, 32.6% females. Lesion location: Trunk: N = 241; extremities: N = 128; head and face: N = 82; palms and soles: N = 10. Histopathologically, 246 pigmented lesions turned out to be melanocytic and 217 were of non-melanocytic origin. Final diagnoses: Malignant lesions: Basal cell carcinoma: N = 72; squamous cell carcinoma: N = 37; melanoma: N = 29. Benign lesions: Melanocytic nevi: N = 217; seborrheic keratosis: N = 43; solar lentigo: N = 37; lichen planus-like keratosis: N = 21, others: N = 7. Inclusion criteria: All pigmented lesions biopsied or excised during a 30-month period. Patients included are only those who received resection. This changes the spectrum of disease as it excludes patients with lesions that were not considered concerning enough to warrant resection. Exclusion criteria: Poor image quality (N = 3). Clinical setting: Primary care skin cancer practice in Queensland, Australia |
| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

#### A. Risk of bias

**Index test**

For each lesion: A triplet of high-resolution digital images consisting of two clinical images (overview and close-up) followed by one dermatoscopic image. The clinical images were taken with Canon EOS digital single lens reflex cameras. The close-up was taken using a macro lens (60-mm f2.8 macro, Canon) with diffuse illumination at a constant reproduction ratio determined by a custom-fabricated spacer. The degree of magnification of the close-up images was similar to that of the dermatoscopy images. Dermatoscopic images were nonpolarising, preferentially using the Dermlite Fluid device (3 Gen, San Juan, Capistrano, Ca); alternatively Dermlite Foto (custom nonpolarised; 3 Gen) and Heine Delta 20 devices (Heines, Optotechnic GmbH< Herrsching, Germany) were used for large and inaccessible lesions, respectively. Dermatoscopic photographs were taken with Canon EOS single lens reflex cameras. Images were presented to the assessors as powerpoint slides. After inspection of the images, the assessor was required to give a diagnosis (criteria not reported, so presumably based on qualitative criteria). Dermatoscopic images were also screened for asymmetry of structure and colour (“chaos”) and for clues to malignancy. Asymmetry of colour and structure were defined according to the basic principles of pattern analysis as revised by Kittler (2007, Dermatopathology: Practical & Conceptual, 13:1). Clues to malignancy included: Eccentric structureless zone (any colour except skin colour), gray or blue structures, peripheral black dots or clods, segmental radial lines or pseudopods,
polymorphous vessels, white lines, thick reticular or branched lines, and parallel lines on ridges (acral lesions). *Not further information regarding the specific cut-off criteria for malignancy reported. The reporting of the results suggests that the test performance is based on best possible scenario.*

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or its interpretation differ from the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
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<td><strong>A. risk of bias</strong></td>
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<tr>
<td>Reference standard(s)</td>
<td>Histopathology</td>
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<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
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<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
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<td><strong>B. Concerns regarding applicability</strong></td>
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<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
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<tr>
<td><strong>FLOW AND TIMING</strong></td>
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<td>Was there an appropriate interval between index test and reference standard?</td>
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<td>Were all patients included in the analysis?</td>
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<td>Could the patient flow have introduced bias?</td>
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<td><strong>NOTES</strong></td>
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The results are presented for all malignancies combined. The 2-by-2 table could not be extracted and the results could not be separated into the different malignancies.

**References**

**Included Studies**

**Excluded Studies**
Abbas Q, Celebi ME, Garcia IF, Rashid M. Lesion border detection in dermoscopy images using dynamic programming. *Skin Research and Technology* 2011;17(1):91-100.
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
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Baade PD, Youl PH, Janda M, Whiteman DC, Del Mar CB, Aitken JF. Factors associated with the number of lesions excised for each skin cancer: a study of primary care physicians in Queensland, Australia. Archives of Dermatology 2008;144(11):1468-76.
Exclusion Reason: Not in PICO

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Carli P, Chiarugi A, De Giorgi V. Examination of lesions (including dermoscopy) without contact with the patient is associated with improper management in about 30% of equivocal melanomas. Dermatologic Surgery 2005;31(2):169-72.
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Cheng A, Bennett A, Pogrel MA, Schmidt BL. Should tumor depth measured from an incisional biopsy be used to guide the decision to perform an elective neck dissection? Journal of Oral and Maxillofacial Surgery 2012;70(9 SUPPL. 2):e-1.
Exclusion Reason: Not in PICO

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Epstein JB, Scully C. Assessing the patient at risk for oral squamous cell carcinoma. [Review] [87 refs]. Special Care in Dentistry 1997;17(4):120-8.
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FitzGerald KL, Buttner PG, Donovan SA. Nonpigmented skin lesions - how many are nonmelanoma skin cancer? Australian Family Physician 2006;35(7):555-7.

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Telemedicine and E-Health, 19: 780-785.
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Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Moreno G, Tran H, Chia ALK, Lim A, Shumack S. Prospective study to assess general practitioners' dermatological diagnostic skills in a referral setting. *Australasian Journal of Dermatology* 2007;48(2):77-82.
Exclusion Reason: Not in PICO

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Myers M, Gurwood AS. Periocular malignancies and primary eye care. [Review] [22 refs]. Optometry (St.Louis, Mo.) 2001;72(11):705-12.
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Exclusion Reason: Narrative Review

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Parkinson RW. Shave biopsies--simple and useful. Postgraduate Medicine 166;84(8):161-70.
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Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)


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Exclusion Reason: Narrative review

Robison Sean, Kljakovic Marjan, Barry Peter. Choosing to biopsy or refer suspicious melanocytic lesions in general practice. BMC Family Practice 2012;13(1):78.
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Sandison A. Common head and neck cases in our consultation referrals: diagnostic dilemmas in inverted papilloma. [Review] [13 refs]. Head and neck pathology 2009;3(3):260-2
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Exclusion Reason: Setting not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: N=1


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO


Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review
Stolte M. [The new "Vienna Classification" for epithelial neoplasia of the gastrointestinal tract. Pros or cons?]. [Review] [34 refs] [German]. Pathologe 2001;22(1):4-12.

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review
Exclusion Reason: Not in PICO
TerKonda SP, Perdikis G. Non-melanotic skin tumors of the upper extremity. [Review] [50 refs]. Hand Clinics 104;20(3):293-301.
Exclusion Reason: Narrative Review
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
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Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO
Exclusion Reason: Narrative Review
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Exclusion Reason: Narrative Review
Exclusion Reason: Not in PICO
Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Narrative Review

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

Exclusion Reason: Not in PICO

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Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Narrative Review


Exclusion Reason: Not in PICO


Exclusion Reason: Narrative Review


Exclusion Reason: Not in PICO: Clinical versus histological diagnosis (not biopsy or dermatoscopy versus histology or follow up)


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: Not in PICO


Exclusion Reason: N=2

Suspected Cancer: Appendix F (June 2015)
HEAD AND NECK CANCERS

LARYNGEAL CANCER

Review question:
What is the risk of laryngeal cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

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</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 7
Study results

No evidence was identified.

References

Included studies
None

Excluded studies (with excl reason)


Narrative review

Narrative review

Not in PICO

Narrative review

Bahar, G., Nageris, B. I., Spitzer, T., Popovtzer, A., Mharshak, G. & Feinmesser, R. (929) [Subglottic carcinoma]. [Review] [33 refs] [Hebrew]. Harefuah, 141: 914-918.
Narrative review

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review


patient-reported speech and swallowing problems in head and neck cancer patients in clinical practice. Supportive Care in Cancer, 20: 2925-2931. Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review


Guideline


Not in PICO (population)


Not in PICO


Not in PICO


Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
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Narrative review
Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO - no method/result section detailing the population
Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

In Serbian without an English abstract. Looks like a narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review
Not in PICO
Not in PICO
Letter
Narrative review
Not in PICO
Narrative review
Not in PICO
Narrative review
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Narrative review
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Not in PICO
Narrative review

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Not in PICO


Narrative review


Not in PICO


Not in PICO

**Review question:**
Which investigations of symptoms of suspected laryngeal cancer should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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<tr>
<td><em>Psychinfo</em></td>
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<td>0</td>
<td>10/04/2013</td>
</tr>
</tbody>
</table>
Study results

No evidence was identified pertaining to the diagnostic accuracy of chest x-ray in patients with suspected laryngeal cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


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Not in PICO
Narrative review

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Laryngology, 270: 398.
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ORAL CANCER

Review question:
What is the risk of oral cancer in patients presenting in primary care with symptom(s)?

Results

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Total References retrieved (after de-duplication): 10
Study results
No evidence was identified.

References

Included studies
None

Excluded studies (with excl reason)

Narrative review

Not in PICO

Not in PICO

Study design not in PICO: Symptom prevalence study (with no case/no case verification) + cancer patient study

Not in PICO
Not in PICO


Not in PICO

Not in PICO

Not in PICO


Not in PICO


Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Nowhere available, but I think it is a narrative review

Narrative review

Not in PICO

Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
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Editorial
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Narrative review
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Narrative review
Narrative review

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Not in PICO

Narrative review

Narrative review

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

of factors associated with early versus late stage oral cavity cancer diagnoses. *Oral Oncology, 47*: 642-647.

Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


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Narrative review

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Narrative review

Not in PICO


Narrative review


Not in PICO


Narrative review

McIntyre, G. T., Oliver, R. J., McIntyre, G. T. & Oliver, R. J. (1999) Update on precancerous lesions. Dental Update, 26: 382-386.

Narrative review


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


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Narrative review


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Not in PICO

Not in PICO
Narrative review

Narrative review

Singh, P. & Warnakulasuriya, S. (2006) The two-week wait cancer initiative on oral cancer; the
Not in PICO

Not in PICO

Not in PICO

Not in PICO

from a health promotion perspective: experience of a diagnosis network in Ceara. - *Pesquisa
Odontologica Brasileira = Brazilian Oral Research*, 28 Spec, 2014..
Only 73/296 leasions were confirmed histologically. The others do not appear to have been
followed up.

Epidemiologia*, 14: 642-650.
Not in PICO

Not in PICO

365-367.
Narrative review

Comment

Narrative review

41: 132-135.
Not in PICO

Narrative review

Oncology*, 45: 692-695.
Not in PICO

Not in PICO

Not in PICO


Review question:
Which investigations of symptoms of suspected oral cancer should be done with clinical responsibility retained by primary care?

Results

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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO
**Risk of bias in the included studies**

The risk of bias and applicability concerns are summarised for the included study in the figure below. The study was associated with a number of bias and validity issues. The following issues compromise the validity and applicability of this study, (1) it is unclear (and probably unlikely) that the patient population consists of consecutive or randomly recruited patients (and may therefore bias the results), (2) the study is conducted in the USA in an unclear setting and it is therefore not clearly transferable to UK-based primary care, and (3) the time span between the index test and reference standard is unclear in all but one patient and the results are therefore compromised to an unknown extent.
Study results

Table 1: Oral cancer: Study results

<table>
<thead>
<tr>
<th>Study</th>
<th>Test</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI) %</th>
<th>Specificity (95% CI) %</th>
<th>Other results (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Svirsky (2002)</td>
<td>Transepithelial oral brush biopsy with a computer-assisted method of analysis</td>
<td>15/298</td>
<td>93.3 (66-99.7)</td>
<td>19.1 (14.8-24.3)</td>
<td>Malignancy: TP = 14 FN = 1 TN = 54 FP = 229 Positive predictive value = 5.76 (3.3-9.7)% Negative predictive value = 98.18 (89-99.9)% False negativity rate = 6.7%</td>
</tr>
<tr>
<td>Svirsky (2002)</td>
<td>Transepithelial oral brush biopsy with a computer-assisted method of analysis</td>
<td>97/298</td>
<td>95.88 (89.2-98.7)%</td>
<td>25.37 (19.6-32.1)%</td>
<td>Malignancy and dysplasia: TP = 93 FN = 4 TN = 51 FP = 150 Positive predictive value = 38.27 (32.2-44.7) % Negative predictive value = 92.73 (81.6-97.6)% False negativity rate = 4.12%</td>
</tr>
</tbody>
</table>

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Evidence statement(s):

Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 93.3%, a specificity of 19.1%, a positive predictive value of 5.76%, and a false negativity rate of 6.7% for oral cancer. Transepithelial oral brush biopsy with a computer-assisted method of analysis (1 study, N = 298) is associated with a sensitivity of 95.88%, a specificity of 25.37%, a positive predictive value of 38.27%, and a false negativity rate of 4.12% for oral cancer/dysplasia. The study was associated with 4 bias or applicability concerns (see also Table 1).

Evidence tables

Svirsky (2002)
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 298 (146 males/152 females), mean (range) age = 52 (18-89); location of surgical biopsy: Ventral/lateral tongue (N = 90), palate (N = 63), gingival (N = 65), buccal/alveolar mucosa (N = 43), floor of mouth (N = 8), unspecified/other (N = 29).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>“This study analyzed scalpel biopsies with test requisition forms that either were accompanied by an oral brush biopsy report or contained the findings of an oral brush biopsy report. Only oral pathology laboratories were included.” “A total of 298 patients with scalpel biopsies that were accompanied by prior brush biopsy results were identified in the authors’ laboratories”.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>None reported.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Unclear, USA</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? Unclear concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Transepithelial oral brush biopsy with a computer-assisted method of analysis (OralCDx, CDx Laboratories, NY).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Unclear concern

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Scalpel biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern
## FLOW AND TIMING

### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>Data are available for all the included patients, but for least one of the patients the brush and scalpel biopsies were obtained 8 months apart.</th>
</tr>
</thead>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
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## NOTES

### References

#### Included studies


#### Excluded studies (with excl reason)

- Reference List
  - Narrative review
  - Guideline
  - Not in PICO
  - Narrative review
  - Not in PICO
  - Not in PICO
  - Narrative review
  - Not in PICO
Pathology & Medicine, 42: 670-675.
Not in PICO

Not in PICO

Not in PICO (On the basis of the clinical diagnostic suspicion and state of dysplasia / carcinoma in 31/67 lesions, while the remaining 35/66 led to a clinical diagnosis of precancerous dysplasia probably without)

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Bentley, R. H., Johnson, S. J. & Sloan, P. (2011) Audit of pre-operative fine needle aspiration cytology (FNAC) for suspected salivary neoplasms. Cytopathology, 22: ii. Published as abstract only. Not enough information available, but I think it is "Not in PICO".

Not in PICO


Not in PICO

Not in PICO

Not in PICO


Guideline


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO (secondary care)


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


113: 1411-1417.
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO
Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO


Not in PICO


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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Same as Mehrotra 2011

Narrative review

Not in PICO

Narrative review

Narrative review
Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO (tests)


Narrative review


Duplicate


Not in PICO


Not in PICO, but included cytopathology papers checked for relevance


Not in PICO


Not in PICO


Not in PICO
Duplicate

Duplicate

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Scala, M., Moresco, L., Comandini, D., Monteghirfo, S. & Tomei, D. (1997) [The role of the general practitioner and dentist in the early diagnosis of preneoplastic and neoplastic lesions of the oral

Suspected Cancer: Appendix F (June 2015)  Page 1299 of 1735
Not in PICO

Not in PICO

Not in PICO

Primary care, but result not reported for index test negative patients (618/945)

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO


Not in PICO


Narrative review

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


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Narrative review


Narrative review


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Narrative review


Narrative review


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Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review
**THYROID CANCER**

**Review question:**
What is the risk of thyroid cancer in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

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<td>Biomed Central</td>
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Total References retrieved (after de-duplication): 274

**Update Search**

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Total References retrieved (after de-duplication): 6
Study results
No evidence was identified.

References

Included studies
None

Excluded studies (with excl reason)

Patient information leaflet
Put down as Narrative review, but not seen. Not available unless we try using a world wide search, which I have decided not to as highly unlikely it will be relevant.
Not in PICO
Not in PICO
Narrative review
Not in PICO
Portuguesa, 21: 135-140.
Not in PICO
Not in PICO
Narrative review
Arbelle, J. E., Shalom, S. I., Benbassat, C., Dickstein, G., Glasser, B. & Liel, Y. (836) [Summary of the Israeli Endocrine Society's consensus statement on the diagnosis, treatment and follow-up of well-differentiated thyroid cancer]. [27 refs] [Hebrew]. Harefuah, 147: 825-832.
Narrative review
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO

Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Narrative review

Narrative review


Narrative review

CHABON, S. L. (505) Identification and evaluation of thyroid nodules. [Review] [8 refs]. *Lippincott’s Primary Care Practice*, 1: 499-504.

Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


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Not in PICO


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Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Guideline/Not in PICO

Goldstein, R. E., Netterville, J. L., Burkey, B. & Johnson, J. E. (2002) Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Guideline


Not in PICO


Narrative review


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Narrative review
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<th>Title</th>
<th>Journal, Volume, Pages</th>
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<tr>
<td>Haynes &amp; -Inc</td>
<td>2013</td>
<td>BRAF p.Val600Glu testing in papillary thyroid carcinoma (Structured abstract).</td>
<td>Health Technology Assessment.Database.</td>
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<td>Huong, J., Menezes, J. &amp; Naqvi, S.</td>
<td>2012</td>
<td>Respiratory failure leading to an unexpected diagnosis of MEN syndrome.</td>
<td>Journal of Hospital Medicine, 7: S216.</td>
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Not in PICO
Not in PICO
Not in PICO/narrative review
Narrative review
Narrative review
Not in PICO
Not in PICO
Narrative review
Not in PICO
Consensus statement/guideline
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Narrative review

Narrative review


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Guideline

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO
Narrative review
Not in PICO
Not in PICO
Narrative review
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO (referred)
Narrative review
Suspected Cancer: Appendix F (June 2015)

Not in PICO (population/outcome [e.g., no distinction between benign & malignant thyroid tumours])


Not in PICO


Narrative review


Narrative review


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Narrative review


Not in PICO


Guideline


Ranganathan, B., Thriyayi, S., Yap, B., Loughran, S. & Homer, J. J. (2012) Regional audit on thyroid cytology reporting. Clinical Otolaryngology, 37: 115. Abstract only, not enough information available to ascertain relevance, but I don’t think it is in PICO


Regional Thyroid Cancer Group (2000) Northern Cancer Network guidelines for management of thyroid cancer. [Review] [155 refs]. Clinical Oncology (Royal College of Radiologists), 12: 373-391. Guideline


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review

Tonjes, A. & Paschke, R. (573) [Diagnosis and therapy of thyroid nodules]. [Review] [22 refs] [German]. *Internist*, 46: 565-572.

Narrative review


Not in PICO

Tuttle, R. M. & Fagin, J. A. (100) Can risk-adapted treatment recommendations replace the 'one size fits all' approach for early-stage thyroid cancer patients? *Oncology (Williston Park)*, 23: 592.

Not in PICO


Not in PICO

Not in PICO

Guideline

Narrative review

Not in PICO

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO

Narrative review

Narrative review

Not in PICO

**Review question:**
Which investigations of symptoms of suspected thyroid cancer should be done with clinical responsibility retained by primary care?

**Results**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references</th>
<th>No of references</th>
<th>Finish date of</th>
</tr>
</thead>
</table>

Suspected Cancer: Appendix F (June 2015)
Study results

No evidence was identified pertaining to the diagnostic accuracy of ultrasound, thyroid function tests, or fine needle aspiration in patients with suspected thyroid cancer where the clinical responsibility was retained by primary care.
References

Included studies
None

Excluded studies (with excl reason)
Reference test not in PICO
Population not in PICO
Not in PICO (secondary care)
Population not in PICO
Population not in PICO
Population not in PICO
Population not in PICO
Narrative review
Population not in PICO
Population not in PICO
Population not in PICO


Population not in PICO


Narrative review


Test not in PICO


Reference test not in PICO


Narrative review


Population not in PICO


Not in PICO


Case series


Narrative review


Population not in PICO


Population not in PICO


Reference test not in PICO


Not in PICO


Not in PICO


Population not in PICO

Reference test not in PICO


Test not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Reference test not in PICO


Narrative review


Narrative review


Narrative review


Reference test not in PICO
Narrative review

Chabon, S. L. (505) Identification and evaluation of thyroid nodules. [Review] [8 refs]. Lippincott’s Primary Care Practice, 1: 499-504.
Narrative review

Reference test not in PICO

Population not in PICO

Population not in PICO

Population not in PICO

Narrative review

Narrative review

Population not in PICO

Not in PICO

Population not in PICO

Population not in PICO

Population not in PICO
Population not in PICO

Narrative review

Population not in PICO

Reference test not in PICO

Narrative review

Test not in PICO

Paper in Chinese with English abstract. Unable to translate the whole paper, but from abstract appear to be in secondary care

Population not in PICO

Population not in PICO

Reference test not in PICO

Narrative review

Population not in PICO

Narrative review

Narrative review


Population not in PICO


Population not in PICO


Population not in PICO


Not in PICO


Population not in PICO


Population not in PICO


Narrative review


Population not in PICO


Narrative review


Not in PICO


Test not in PICO


Narrative review


Narrative review


Narrative review


Population not in PICO

papillary or follicular thyroid cancer (DARE structured abstract). *Journal of Clinical Endocrinology and Metabolism*, 86: 3779-3786.

Test not in PICO


Population not in PICO


Not in PICO


Population not in PICO


Narrative review


Narrative review


Narrative review


Test not in PICO


Not in PICO


Test not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO
Population not in PICO

Reference test not in PICO

Population not in PICO

Case series

Narrative review

Not in PICO

Narrative review

Population not in PICO

Reference test not in PICO

Population not in PICO

Population not in PICO

Not in PICO

Narrative review

Population not in PICO
Narrative review

Test not in PICO

Narrative review

Population not in PICO

Population not in PICO

Population not in PICO

Population not in PICO

Population not in PICO

Narrative review

Population not in PICO

Reference test not in PICO

Narrative review

Population not in PICO


Not in PICO (population/outcome [e.g., no distinction between benign & malignant thyroid tumours])

Population not in PICO

Population not in PICO

Population not in PICO

Narrative review

Population not in PICO

Population not in PICO

Narrative review

Population not in PICO

Narrative review

Population not in PICO

Population not in PICO

Not in PICO
Test not in PICO
Abstract only, not enough information available to ascertain relevance, but I don't think it is in PICO
Reference test not in PICO
Population not in PICO
Narrative review
Population not in PICO
Case series
Not in PICO
Narrative review
Narrative review
Reference test not in PICO
Population not in PICO
Narrative review
Population not in PICO

Reference test not in PICO


Not in PICO


Population not in PICO


Narrative review


Population not in PICO


Reference test not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO


Population not in PICO

24: 44-47.

Population not in PICO


Narrative review


Population not in PICO


Population not in PICO


Narrative review


Population not in PICO


Population not in PICO


Population not in PICO


Narrative review

Tonjes, A. & Paschke, R. (573) [Diagnosis and therapy of thyroid nodules]. [Review] [22 refs] [German]. *Internist*, 46: 565-572.

Narrative review


Population not in PICO


Population not in PICO


Population not in PICO


Not in PICO


Not in PICO (secondary care)

Population not in PICO


Population not in PICO


Population not in PICO


Narrative review


Reference test not in PICO


Narrative review


Population not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO

Wolinski, K., Szkudlarek, M., Szczepanek-Parul ska, E. & Ruchala, M. (2014) - Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta-analysis of

Not in PICO


Narrative review


Reference test not in PICO


Population not in PICO
BRAIN AND CENTRAL NERVOUS SYSTEM CANCERS

Review question:
What is the risk of brain and CNS cancer in patients presenting in primary care with symptom(s)?

Results

Literature search

<table>
<thead>
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Total References retrieved (after de-duplication): 277

Update Search

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<td>58</td>
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<td>6</td>
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<tr>
<td>Cochrane Library</td>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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<td>87</td>
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Total References retrieved (after de-duplication): 19
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that a number of the studies employed case-control (or other non-consecutive, non-randomised) designs which have been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Other issues of concern include that some of the studies were conducted abroad and their direct relevance to UK-based primary care may therefore be limited, that the symptoms were underspecified in one study and therefore of limited use for the present purposes, and that some of the reference standards employed were of questionable quality and applicability.

Study results
Table 1: Brain & CNS cancer: Study results for adult populations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value % (95% CI)</th>
<th>Frequency</th>
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<td><strong>Hamilton (2007)</strong></td>
<td>Headache</td>
<td>All patients</td>
<td>0.09 (0.08-0.1)</td>
<td>Cases: 362/3505 Controls: 261/24021</td>
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<td><strong>Hamilton (2007)</strong></td>
<td>Headache*</td>
<td>Patients 60-69 years</td>
<td>0.12 (NR)</td>
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<tr>
<td><strong>Kernick (2008)</strong></td>
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<td>All patients</td>
<td>0.15 (0.12-0.19)</td>
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<td>0.08 (0.05-0.11)</td>
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<td><strong>Kernick (2008)</strong></td>
<td>Undifferentiated headache</td>
<td>Patients ≥ 50 years</td>
<td>0.28 (0.22-0.36)</td>
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<tr>
<td><strong>Kernick (2008)</strong></td>
<td>Primary headache</td>
<td>All patients</td>
<td>0.045 (0.023-0.088)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Symptom(s)</td>
<td>Patient group</td>
<td>Positive predictive value % (95% CI)</td>
<td>Frequency</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>--------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.055 (0.047-0.065)</td>
<td>Cases: 342/1267, Control: 211/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.07 (0.064-0.078)</td>
<td>Cases: 427/1267, Control: 829/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Neurological symptoms 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.083 (0.067-0.105)</td>
<td>Cases: 108/1267, Control: 207/15318</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Headache 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.064 (0.051-0.082)</td>
<td>Cases: 90/1267, Control: 224/15318</td>
</tr>
</tbody>
</table>

Table 2: Brain & CNS cancer: Positive predictive values for any childhood cancer: Patients aged 0-14 years

* Peak PPVs for these symptoms are in this age group.
<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Symptom Description</th>
<th>Population</th>
<th>All patients</th>
<th>OR (95% CI)</th>
<th>Cases</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Headache 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.06 (0.04-0.08)</td>
<td>73</td>
<td>55/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Headache 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.13 (0.08-0.22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lymphadenopathy 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.096 (0.074-0.126)</td>
<td>82</td>
<td>136/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.09 (0.06-0.13)</td>
<td>69</td>
<td>33/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All patients</td>
<td>0.2 (0.1-0.39)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lump/mass/swelling 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.172 (0.119-0.25)</td>
<td>56</td>
<td>52/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.11 (0.06-0.2)</td>
<td>42</td>
<td>16/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump/mass/swelling below neck excluding abdomen 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.3 (0.09-0.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Fatigue 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.085 (0.06-0.121)</td>
<td>47</td>
<td>88/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.07 (0.04-0.12)</td>
<td>42</td>
<td>24/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-12 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.12 (0.06-0.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Back pain 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.088 (0.06-0.128)</td>
<td>40</td>
<td>73/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Bruising 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.08 (0.054-0.118)</td>
<td>38</td>
<td>76/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.08 (0.05-0.13)</td>
<td>33</td>
<td>18/15318</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.38 (0.09-1.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.41 (0.12-1.34)</td>
<td>33</td>
<td>18/15318</td>
<td></td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Symptom Description</td>
<td>Population</td>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
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<tr>
<td>-------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.76 (0.1-5.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.3 (0.1-0.84) Cases: 28/1267 Control: 4/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All patients</td>
<td>0.76 (0.1-5.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Abnormal movement 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.08 (0.04-0.14) Cases: 49/1267 Control: 26/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Abnormal movement 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.15 (0.07-0.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bleeding 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bleeding 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.11 (0.04-0.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Visual symptoms 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.06 (0.03-0.1) Cases: 28/1267 Control: 21/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Visual symptoms 0-3 months before diagnosis and ≤ 3 consultations</td>
<td>All patients</td>
<td>0.23 (0.07-0.77)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.04 (0.03-0.06) Cases: 42/1267 Control: 41/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.14 (0.07-0.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All patients</td>
<td>0.04 (0.03-0.07) Cases: 107/1267 Control: 102/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis and ≥ 3 consultations</td>
<td>All patients</td>
<td>0.13 (0.08-0.19)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Urinary symptoms 0-12 months before diagnosis</td>
<td>All patients</td>
<td>0.266 (0.117-0.609) Cases: 15/1267 Control: 9/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All patients</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Childhood infection 0-3 months before diagnosis</td>
<td>All patients</td>
<td>Cases: 54/1267 Control: 236/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Upper respiratory tract infection 0-3 months before diagnosis</td>
<td>All patients</td>
<td>Cases: 143/1267 Control: 942/15318</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Symptom(s)</td>
<td>Patient group</td>
<td>Positive predictive value % (95% CI) Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------------------------------</td>
<td>----------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Abnormal movement 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.11 (0.03-0.35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Visual symptoms 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.07 (0.02-0.24)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Vomiting 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.04 (0.02-0.07)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ansell (2009)</td>
<td>Vomiting and unsteadiness</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.15 (0.01-0.1) 1/654</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ansell (2009)</td>
<td>Vomiting and visual difficulties</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.088 (0.005-0.6) 1/1142</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ansell (2009)</td>
<td>Headache and unsteadiness</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.085 (0.005-0.6) 1/1172</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The positive predictive values are calculated using Bayesian statistics.

Table 3: Brain & CNS cancer: Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour
Ansell (2009)  
“All other symptom combinations (except vomiting or headache with anorexia) had a predictive probability [of a child having a brain tumour given a visit to a GP with both symptoms] of between 1 in 1500 and 1 in 8000 children”. The predictive probabilities of vomiting or headache with anorexia appeared to be even lower.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Symptom Description</th>
<th>Population Description</th>
<th>Predictive Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Headache 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.03 (0.02-0.06)</td>
</tr>
<tr>
<td>Kernick (2009)</td>
<td>Headache (any type)</td>
<td>All patients aged 5-17 years</td>
<td>0.03 (0.01-0.05)</td>
</tr>
<tr>
<td>Kernick (2009)</td>
<td>Primary headache</td>
<td>All patients aged 5-17 years</td>
<td>0 (0-0.05)</td>
</tr>
<tr>
<td>Kernick (2009)</td>
<td>Undifferentiated headache</td>
<td>All patients aged 5-17 years</td>
<td>0.03 (0.02-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.08)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Seizure 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.02 (0.01-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Seizure</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0238 (0.0082-0.0695)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Headache</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0145 (0.0077-0.0276)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Vomiting</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0116 (0.0041-0.031)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Pain</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0029 (0.0014-0.006)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Visual symptoms</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>Cases: 8.4% Controls: 0%</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>≥ 3 consultations</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0023 (0.0019-0.0029)</td>
</tr>
</tbody>
</table>
The positive predictive values are calculated using Bayesian statistics.

Evidence statement(s):

The positive predictive values of having a brain tumour in adulthood ranged from 0% (for dizziness and/or weakness) to 2.3% (for new-onset seizure in 60-69 year old patients) for symptomatic patients presenting to primary care (4 studies, N = 106588). The included studies were associated with 0-4 bias/applicability concerns each (see also Table 1).

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain or musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) for symptomatic patients aged 0-14 years old presenting to primary care (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 2).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from < 0.013% (for vomiting or headache with anorexia) to 0.15 (for vomiting in combination with unsteadiness) for patients aged 0-14 years old, from 0% (for primary headache) to 0.03% (for undifferentiated headache) for patients aged 5-17 years, and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (3 studies, N = 79910). The evidence quality is somewhat compromised by the case-control design of two of the studies (see also Table 3).

Evidence tables

Ansell (2009)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
<th>National population-based case-control study (United Kingdom Childhood Cancer Study; UKCCS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td></td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td></td>
</tr>
<tr>
<td>Cases:</td>
<td>195 children; mean (SE) age = 7.31 (0.27) years; 93 males/102 females; astrocystoma: N = 78; medulloblastoma: N = 46; other: N = 71.</td>
</tr>
<tr>
<td>Controls:</td>
<td>285 children; mean (SE) age = 7.25 (0.22) years; 142 males/143 females;</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Cases: Children aged 0–14 years newly diagnosed with cancer between 1992-1996 in Great Britain were eligible to take part. Children with brain tumours were recruited from 1992-1994. These data were systematically collected</td>
</tr>
</tbody>
</table>
from primary care records by 4 of the 10 UKCCS regions: “GP records were abstracted for 195 of 221 (88%) children with brain tumours and for 286 controls.” Controls: (1-?)2 gender-, month and year of birth-, and region of residence-matched controls were randomly recruited from primary care population registers.
Exclusion criteria: None listed
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

**Index test**

Relevant signs and symptoms were defined as those that might be suggestive of a brain tumour: Anorexia, abnormal movements, back problems, cognitive impairment, congenital anomalies, drowsiness, emotional problems, focal weakness, growth problems, head tilt, headache, hearing problems, hydrocephalus, incontinence, papilloedema, problem behaviour, seizures, unsteady on feet, visual problems, vomiting, other neurological signs and symptoms not already included.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>
| **For diagnostic case-control studies:**
Investigators were kept 'blind' to other important confounding and prognostic factors? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

#### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**

Cancer diagnosis or not in their General Practice record.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. Risk of bias

**Flow and timing**

All patients appear to be accounted for.

| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
Were all patients included in the analysis? | Yes
---|---
Could the patient flow have introduced bias? | Low risk

**NOTES**

Dommett (2012; 2013a,b)

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

| Attempts were made within the design or analysis to balance the comparison groups for potential confounders? | Yes |
| The groups were comparable at baseline, including all major confounding and prognostic factors? | Yes |

**Could the selection of patients have introduced bias?** | High risk

### B. Concerns regarding applicability

**Patient characteristics and setting**

| Cases: | 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: | Up to 13 controls (children with no diagnosis of cancer at any time) |
| Controls: | 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported |

**Inclusion criteria:**

The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls.

Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.

Controls: Up to 13 controls (children with no diagnosis of cancer at any time).
were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date).

Exclusion criteria: None listed

Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
</tr>
<tr>
<td>The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. <em>No more information reported.</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

*For diagnostic case-control studies:* Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference standard(s)</strong></td>
</tr>
<tr>
<td>Cancer diagnosis in the UK's General Practice Research Database.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow and timing</strong></td>
</tr>
<tr>
<td>All patients appear to be accounted for.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were all patients included in the analysis?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the patient flow have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**NOTES**

This study is published in three papers. There is almost complete overlap between the patients used in Kernick (2009) with the patients aged 5-17 years in this study.
### Hamilton (2007)

#### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases: 3505 patients with 2397 malignant tumours (incl 948 gliomas and 280 astrocytomias, and other rare tumours; the rest were benign); aged 18-29 years: N = 159 (malignant tumours N = 134); aged 30-39 years: N = 276 (malignant tumours N = 206); aged 40-49 years: N = 432 (malignant tumours N = 280); aged 50-59 years: N = 675 (malignant tumours N = 471); aged 60-69 years: N = 822 (malignant tumours N = 584); aged 70-79 years: N = 767 (malignant tumours N = 511); aged 80-89 years: N = 339 (malignant tumours N = 191); aged &gt;90 years: N = 35 (malignant tumours N = 20); 1661 males/1844 females. Controls: N = 17173 or 24824</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Cases: Patients aged 18 years or over with a brain tumour diagnosed between May 1988 and March 2006, and with at least 2 years of data before the first tumour code (the index date), who had consulted at least once within the 6 months before the index date Controls: 7 randomly selected, practice-, sex- and age (within 1 year)-matched controls were selected per case, who had consulted at least once within the 6 months before the index date.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Controls: Prior brain tumour.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Primary care, UK.</td>
</tr>
</tbody>
</table>

| Could the selection of patients have introduced bias? | High risk |

#### INDEX TEST

**A. Risk of bias**

| Index test | “Libraries of codes for clinical variables previously described with brain tumours were assembled... Occurrences of these variables in the 6 months before the index date in cases and controls were identified. Variables were retained only if they occurred in at least 1% of cases or controls... Re-consultations with the same symptom were also retained if the subsequent...” |

---

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A symptom was also present in 1% or more cases or controls. No restriction was placed on reporting of the variable before the 6 month period of study, except for seizures which were only used if the patient had no previous seizure or anticonvulsant therapy code in their records.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td>Yes</td>
</tr>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Brain tumour diagnosis in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

This study includes a significant minority with benign tumours (see “Patient characteristics and setting” above).

**Herr (1989)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series from a North American hospital emergency department</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

**Patient characteristics and setting**

137 patients “representing 46% of the logbook entries for dizziness over this period”; 12 patients were excluded due to missing data leaving 125 patients; 51 males/73 females; mean age (range) = 46.9 (18-82) years.

**Inclusion criteria:**

“From March 1, 1986, to August 1, 1987, we sought consecutive patients presenting to the Northwestern Memorial Hospital ED with a chief complaint of “dizzy,” “lightheaded,” “faint,” or synonymous phrase. Each was required to have one or more attributes of dizziness as described by Drachman and Hart [ref given] (Figure 1*). Syncope, medical problems, or previous dizziness were not exclusions provided dizziness was among the presenting chief complaints.” *A definite rotational sensation; a sensation of impending faint or loss of consciousness; disequilibrium or loss of balance without head sensation; ill-defined “lightheadedness” other than vertigo, syncope, or disequilibrium.

**Exclusion criteria:** None listed

**Clinical setting:** Hospital emergency department, USA.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>High concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

**Index test**

Chief complaint of “dizzy,” “lightheaded,” “faint,” or synonymous phrase, with one or more of the following attributes of dizziness: A definite rotational sensation; a sensation of impending faint or loss of consciousness; disequilibrium or loss of balance without head sensation; ill-defined “lightheadedness” other than vertigo, syncope, or disequilibrium.

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

### B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Low concern

### REFERENCE STANDARD

#### A. risk of bias

**Reference standard(s)**

Emergency physicians’ diagnosis and minimum 1-4 weeks follow up.

| Is the reference standard likely to correctly classify the target condition? | Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk |

### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

Unclear concern

### FLOW AND TIMING
## A. Risk of Bias

### Flow and Timing
- All patients appear to be accounted for.

### Was there an appropriate interval between index test and reference standard?
- Yes

### Did all patients receive the same reference standard?
- Yes

### Were all patients included in the analysis?
- Yes

### Could the patient flow have introduced bias?
- Low risk

## Notes

Kernick (2008)

## Patient Selection

### A. Risk of Bias

#### Patient Sampling
- Cases [patients with a code of headache in their records] from a case-control study using data from the General Practice Research Database (GPRD)

#### Was a consecutive or random sample of patients enrolled?
- Yes

#### Was a case-control design avoided?
- Yes

#### Did the study avoid inappropriate exclusions?
- Yes

#### Could the selection of patients have introduced bias?
- Low risk

### B. Concerns Regarding Applicability

| Patient Characteristics and Setting | 85679 patients with a primary or undifferentiated headache:  
Primary headache: N = 21758, with migraine (N = 15891), tension-type headache (N = 4987), and cluster headache (N = 880); 5795 males/15963 females; median (IQR) age = 38 (29-50) years.  
Undifferentiated headache: N = 63921; 23200 males/40721 females; median (IQR) age = 41 (30-58) years.  
Inclusion criteria: Patients were aged 18 years or over, with a description of headache in their records and no other headache classification code in the previous year. Patients were accepted from the inception of the database in January 1987 to June 2005 who had at least 1 year of full data in their records after the index headache consultation.  
Exclusion criteria: Patients with a secondary headache that had a further descriptor.  
Clinical setting: Primary care, UK. |

### Are There Concerns That the Included Patients and Setting Do Not Match the Review Question?
- Low concern

## Index Test

### A. Risk of Bias

#### Index Test
- Index headache codes were categorised into primary headache (migraine, tension-type headache, or cluster headache). Secondary headaches that had a further descriptor were discarded. All other codes were classified as undifferentiated headache.

#### Were the index test results interpreted without knowledge of the results of the reference standard?
- Yes

#### For diagnostic case-control studies:
- Investigators were kept 'blind' to other important confounding and prognostic factors?
- Yes
<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td></td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Headache-related outcome/diagnosis in the UK’s General Practice Research Database in the year after the index consultation.</td>
<td></td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
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</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
<td></td>
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<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
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<td></td>
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<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
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<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
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</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients appear to be accounted for.</td>
<td></td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
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<td></td>
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<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
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<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td><strong>NOTES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kernick (2009)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PATIENT SELECTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Cases [patients with a code of headache in their records] from a case-control study using data from the General Practice Research Database (GPRD)</td>
<td></td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>48575 patients with a primary, secondary or undifferentiated headache (21180 males/27395 females; age bands: 5-8 years: N = 3623; 9-12 years: N = 13804; 13-17 years: N = 31148): Primary headache: N = 9321, with migraine (N = 7468), tension-type headache (N = 1565), and cluster headache (N = 288); Secondary headache: N = 549; Undifferentiated headache: N = 38705.</td>
<td></td>
</tr>
</tbody>
</table>
**Inclusion criteria:** Patients were aged 5-17 years, with a description of headache in their records and no other headache classification code in the previous year. Patients were accepted from the inception of the database in January 1987 to June 2005 who had at least 1 year of full data in their records after the index headache consultation.  
**Exclusion criteria:** None listed.  
**Clinical setting:** Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**  
Index headache codes were categorised into primary headache (migraine, tension-type headache, or cluster headache) or secondary headaches if they had a further descriptor. All other codes were classified as undifferentiated headache.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

**For diagnostic case-control studies:**  
Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**  
Headache-related outcome/diagnosis in the UK’s General Practice Research Database in the year after the index consultation.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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</table>

<table>
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**B. Concerns regarding applicability**

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<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

**Flow and timing**  
All patients appear to be accounted for.

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Could the patient flow have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>
### NOTES
There is almost complete overlap between the patients used in this study and the patients aged 5-17 years in Dommett (2012, 2013a,b).

### Skiendzielewski (1980)

#### PATIENT SELECTION

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series from a North American hospital emergency department</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

106 patients; ca 35% were aged < 30 years; age range = 7-88 years; 38 males/68 females; N = 10 with weakness only, N = 85 with dizziness, and N = 15 with a combination of weakness and dizziness.

**Inclusion criteria:**
“We retrospectively studied the cases of 106 patients who presented to the Geisinger Medical Center Emergency Department with the chief complaints of weakness and/or dizziness during a six-month period. The patients were examined by a number of physicians whose experience varied from that of a first-year resident to a staff emergency physician”.

**Exclusion criteria:** Cases with specific muscle weakness, e.g., paralysis of a limb.

**Clinical setting:** Hospital emergency department, USA.

**Are there concerns that the included patients and setting do not match the review question?**

High concern

#### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Weakness and/or dizziness. Special attention was given to the presence of true vertigo, current medications, physical findings, abnormal laboratory data, and diagnosis on discharge.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

Unclear concern

#### REFERENCE STANDARD

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>“Follow-up was obtained either from records of subsequent outpatient visits or, more frequently, from personal telephone conversations.” 1-7 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
</tbody>
</table>
Could the reference standard, its conduct, or its interpretation have introduced bias? | High risk  
---|---

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? | Unclear concern

**FLOW AND TIMING**

**A. risk of bias**

Flow and timing | All patients appear to be accounted for.
Was there an appropriate interval between index test and reference standard? | Yes
Did all patients receive the same reference standard? | Yes
Were all patients included in the analysis? | Yes
Could the patient flow have introduced bias? | Low risk

**NOTES**

**References**

**Included studies**


**Excluded studies (with excl reason)**


Not in PICO


Narrative review
Not in PICO

Not in PICO


Alvord, L. S. & Herr, R. D. (1994) ENG in the emergency rom: Subtest results in acutely dizzy patients. J AM Acad Audiol, 5: 384-389. Not in PICO: 21.5% (20/91) patients had unknown diagnosis, final 4-week diagnosis was based on 4-week follow up, and no consistent reference standard.


Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

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Narrative review

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Guideline

Not in PICO

Narrative review

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Narrative review

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Narrative review

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Narrative review

Not in PICO

Semi-systematic review, have checked included studies for relevance


Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO (no reference standard)

Kernick, D., Williams, S., Kernick, D. & Williams, S. (2011) Should GPs have direct access to neuroradiological investigation when adults present with headache? British Journal of General Practice, 61: 409-411.
Narrative review

Narrative review

Narrative review

Narrative review

Not in PICO
*Ceska a Slovenska Oftalmologie,* 60: 348-355.
Not in PICO

Semi-systematic review, have checked included studies for relevance

Not in PICO (reference standard)

Not in PICO

Not in PICO

Guideline

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Narrative review

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Narrative review

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Narrative review

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Narrative review

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Academic Emergency Medicine, 12: 33-37.
Not in PICO
Narrative review
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Narrative review


Narrative review


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Narrative review


Not in PICO

<table>
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<th>Practice, 16: 143-148. Not in PICO</th>
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Narrative review

Narrative review

Narrative review

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Narrative review
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Narrative review

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Narrative review

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Not in PICO

Review question:
Which investigations of symptoms of suspected brain and CNS cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

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<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
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<td>1980-6/2013</td>
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<td>Embase</td>
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<td>2171</td>
<td>90</td>
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<tr>
<td>Cochrane Library</td>
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<td>209</td>
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<td>Psychinfo</td>
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<td>62</td>
<td>2</td>
<td>17/02/2013</td>
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<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>1980-6/2013</td>
<td>57</td>
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Total References retrieved (after de-duplication): 162

Update Search

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<td>22</td>
<td>0</td>
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</tbody>
</table>

Total References retrieved (after de-duplication): 5
Study results

No evidence was identified pertaining to the diagnostic accuracy of CT or MRI scans in patients with suspected brain or CNS cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)
Not in PICO
Narrative review
Abstract only. Not in PICO.
Not in PICO
Narrative review
Not in PICO
Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO (no reference standard for the CT-negative patients)

Not in PICO

Narrative review

Not in PICO

Guideline

Not in PICO

Not in PICO

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Narrative review


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Narrative review


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Guideline

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Narrative review

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Narrative review

Not in PICO (very specific brain tumours)

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Narrative review


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Narrative review


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Narrative review


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Narrative review
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Narrative review
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Not in PICO
Molassiotis, A., Wilson, B., Brunton, L. & Chandler, C. Mapping patients' experiences from initial change in health to cancer diagnosis: A qualitative exploration of patient and system factors mediating this process. [References]. European Journal of Cancer Care 19[1], 98-109. 2010. Not in PICO
Narrative review


Papanikolaou, V., Khan, M. H. & Keogh, I. J. (2010) Incidental findings on MRI scans of patients presenting with audiovestibular symptoms. BMC Ear, Nose and Throat Disorders, 10. Not in PICO


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Narrative review

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Guideline


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HAEMATOLOGICAL CANCERS

LEUKEMIA

Review question:
What is the risk of leukaemia in adults and children presenting in primary care with symptom(s)?

Results

Literature search

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
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<td>1689</td>
<td>42</td>
<td>11/03/2013</td>
</tr>
<tr>
<td>Premedline</td>
<td>All-2012</td>
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<td>1</td>
<td>11/03/2013</td>
</tr>
<tr>
<td>Embase</td>
<td>All-2012</td>
<td>3598</td>
<td>57</td>
<td>13/03/2013</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>All-2012</td>
<td>427</td>
<td>0</td>
<td>13/03/2013</td>
</tr>
<tr>
<td>Psychinfo</td>
<td>All-2012</td>
<td>12</td>
<td>0</td>
<td>11/03/2013</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>All-2012</td>
<td>648</td>
<td>10</td>
<td>18/03/2013</td>
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</table>

Total References retrieved (after de-duplication): 98

Update Search

<table>
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<th>Database name</th>
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<th>No of references retrieved</th>
<th>Finish date of search</th>
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<td>3/2013-18/08/2014</td>
<td>88</td>
<td>0</td>
<td>18/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>3/2013-18/08/2014</td>
<td>135</td>
<td>3</td>
<td>18/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 9
Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included studies in the figure below. One main issue to note is that one study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Another potential threat to the applicability of the findings concerns the fact that the second study employed a patient sample which may not be directly applicable to the current question.

Study results

Table 1: Leukaemia: Positive predictive values for leukaemia/lymphoma childhood cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.53 (0.07-3.91)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before</td>
<td>All included leukemia/lymphoma patients</td>
<td>0.43 (0.06-3.15)</td>
</tr>
</tbody>
</table>
### Table 2: Leukaemia: Positive predictive values for teenage and young adult, and adult leukaemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013b)</td>
<td>Bruising</td>
<td>All leukaemia patients and controls aged 15-24 years</td>
<td>0.0117 (0.004-0.0343) Cases: 9/143</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.35 (0.05-2.65)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.07 (0.03-0.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.06 (0.04-0.11)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.05 (0.02-0.13)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bleeding 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.08)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.02 (0.01-0.03)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fever 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0.01-0.01)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Abdominal pain 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0.01-0.01)</td>
</tr>
</tbody>
</table>

The positive predictive values are calculated using Bayesian statistics.
### Evidence statement(s):

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years (1 study, N = 30855), and the positive predictive value of having adulthood leukaemia was 0.04% (for dyspepsia) for patients aged > 40 years (1 study, N = 2585). Both studies were associated with 1 bias/applicability concern (see also Tables 1-2).

### Evidence tables

**Dommett (2013a,b)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Condition</th>
<th>Group Description</th>
<th>Positive Predictive Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013b)</td>
<td>Fatigue</td>
<td>All leukaemia patients and controls aged 15-24 years</td>
<td>0.0121 (0.0052-0.0282)</td>
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<tr>
<td>Dommett (2013b)</td>
<td>Lymphadenopathy</td>
<td>All leukaemia patients and controls aged 15-24 years</td>
<td>0.0151 (0.004-0.0578)</td>
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<tr>
<td>Dommett (2013b)</td>
<td>≥ 3 consultations</td>
<td>All leukaemia patients and controls aged 15-24 years</td>
<td>0.0038 (0.003-0.0048)</td>
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<tr>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.04 (0.002-0.3)</td>
</tr>
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</table>

The positive predictive values are calculated using Bayesian statistics for Dommett (2013b).
other ICD codes: N = 132.

1064 teenagers and young adults (TYA): 15-24 years: Gender not reported.
Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17).

Controls:
15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females.
13206 TYA. Gender not reported

Inclusion criteria:
The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls.
Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.
Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date).

Exclusion criteria: None listed

Clinical setting: Primary care, UK.

| Are there concerns that the included patients and setting do not match the review question? | Low concern |
| INDEX TEST | 
| A. Risk of bias | 
| Index test | The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. No more information reported. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |
| B. Concerns regarding applicability | 
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

REFERENCE STANDARD
A. Risk of bias
### Reference standard(s)

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
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<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
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### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
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<tbody>
<tr>
<td>Flow and timing</td>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
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<td>Did all patients receive the same reference standard?</td>
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<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
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### NOTES

This study is published in three papers.

Hallissey (1990)

### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
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<tbody>
<tr>
<td>Patient sampling</td>
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<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
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<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
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<tr>
<td>Could the selection of patients have introduced bias?</td>
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### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2585 aged &gt; 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia.</td>
</tr>
<tr>
<td>Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia.</td>
</tr>
<tr>
<td>Exclusion criteria: None listed.</td>
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<tr>
<td>Clinical setting: Primary care, England.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
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### INDEX TEST

<table>
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<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
</tbody>
</table>
### Could the conduct or interpretation of the index test have introduced bias?  
**Low risk**

### B. Concerns regarding applicability

### Are there concerns that the index test, its conduct, or interpretation differ from the review question?  
**Low concern**

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 4 weeks and follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

### Are there concerns that the target condition as defined by the reference standard does not match the question?  
**Low concern**

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>2659 patients were seen and 2585 attended for investigation</th>
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</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
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<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
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### NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), circinomatosis of unknown primary (7).

### References

#### Included studies


#### Excluded studies (with excl reason)

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Narrative review
Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Duplicate

Duplicate

Narrative review/guideline

Not in PICO

Not in PICO
Narrative review

Duplicate

Duplicate

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO


Narrative review
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Not in PICO
Narrative review
Not in PICO
Not in PICO
Not in PICO (secondary care)
Narrative review


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Review question:
Which investigations of symptoms of suspected leukemia should be done with clinical responsibility retained by primary care?

Results

Literature search

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<tr>
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<th>No of references found</th>
<th>No of references retrieved</th>
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<td>Embase</td>
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Update Search

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Total References retrieved (after de-duplication): 6
Study results

No evidence was identified pertaining to the diagnostic accuracy of white blood cell count in patients with suspected leukaemia where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)
Not in PICO
Narrative review
Narrative review
Narrative review
Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Duplicate


Not in PICO


Already included

Anales de Pediatria, 61: 393-397.
Not in PICO
Not in PICO
Not in PICO
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Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Not in PICO


Guideline


Narrative review


Narrative review


Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO
MYELOMA

Review question:
What is the risk of myeloma in patients presenting in primary care with symptom(s)?

Results

Literature search results

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<td>Premedline</td>
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Total references retrieved (after de-duplication): 60

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</tr>
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<td>4/2013-19/08/2014</td>
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<td>2</td>
<td>19/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 6

Study flow diagram
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issues to note are (1) that two of the studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and (2) that two of the studies employed patient selection methods that were not clearly consecutive or random in nature, which, in turn, may result in inflated estimates of the positive predictive values. However, the statistics employed by Shephard (2014) may have gone some way in counteracting this influence.

Risk of bias summary

![Risk of Bias Summary Table]

Study results

Table 1: Myeloma: Positive predictive values of individual symptoms for myeloma in patients aged > 14-15 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>PPV % (95% CI) for myeloma; prevalence of myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyo (1988)</td>
<td>Back pain</td>
<td>All patients</td>
<td>0.05 (0.003-0.3); 1/1975</td>
</tr>
<tr>
<td>Suarez-Almazor (1997)</td>
<td>Acute low back pain</td>
<td>All patients</td>
<td>0 (0-0.5) or 0.21 (0.04-0.83) 0-2/963 Unclear if diagnosis was prior to symptom</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain</td>
<td>Patients ≥ 60 years</td>
<td>0.05 (0.04-0.06)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Shortness of breath</td>
<td>Patients ≥ 60 years</td>
<td>0.06 (0.05-0.06)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Chest infection</td>
<td>Patients ≥ 60 years</td>
<td>0.06 (0.05-0.06)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Chest pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.09-0.11)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Fracture</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.08-0.12)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.08-0.12)</td>
</tr>
</tbody>
</table>
Shephard (2014) | Combined bone pain | Patients ≥ 60 years | 0.1 (0.1-0.2)
Shephard (2014) | Nosebleeds | Patients ≥ 60 years | 0.1 (0.1-0.2)
Shephard (2014) | Back pain | Patients ≥ 60 years | 0.1 (0.1-0.2)
Shephard (2014) | Weight loss | Patients ≥ 60 years | 0.2 (0.1-0.2)
Shephard (2014) | Rib pain | Patients ≥ 60 years | 0.2 (0.1-0.3)
Shephard (2014) | Low haemoglobin | Patients ≥ 60 years | 0.17 (0.16-0.19)
Shephard (2014) | Leucopenia | Patients ≥ 60 years | 0.3 (0.2-0.3)
Shephard (2014) | Low platelets | Patients ≥ 60 years | 0.2 (0.1-0.2)
Shephard (2014) | Raised inflammatory markers | Patients ≥ 60 years | 0.2 (0.18-0.22)
Shephard (2014) | Raised creatinine | Patients ≥ 60 years | 0.08 (0.08-0.09)
Shephard (2014) | Raised MVC | Patients ≥ 60 years | 0.18 (0.16-0.22)
Shephard (2014) | Hypercalcaemia | Patients ≥ 60 years | 0.7 (0.5-1)

**Abbreviations:** CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives; NR, Not reported.

**Table 2: Myeloma: Positive predictive value of symptom combinations for myeloma in patients aged > 14-15 years**

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>PPV % (95% CI) for myeloma; prevalence of myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and shortness of breath</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and chest infection</td>
<td>Patients ≥ 60 years</td>
<td>0.3 (NR)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and chest pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (NR)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and fracture</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (NR)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and nausea</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (NR)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and combined bone pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (NR)</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and nosebleeds</td>
<td>Patients ≥ 60 years</td>
<td>Non-calculable</td>
</tr>
<tr>
<td>Shephard (2014)</td>
<td>Joint pain and back pain</td>
<td>Patients ≥ 60 years</td>
<td>0.1 (0.1-0.2)</td>
</tr>
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<td>Shephard (2014)</td>
<td>Joint pain and</td>
<td>Patients ≥ 60 years</td>
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</tr>
<tr>
<td>Shephard (2014)</td>
<td>Weight or symptom</td>
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<td>Odds ratio (CI)</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------------------------------</td>
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</tr>
<tr>
<td></td>
<td>weight loss</td>
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</tr>
<tr>
<td></td>
<td>Joint pain and rib pain</td>
<td></td>
<td>0.7 (NR)</td>
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<tr>
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<tr>
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<tr>
<td></td>
<td>Shortness of breath and fracture</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Shortness of breath and nausea</td>
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<td>0.2 (0.1-0.3)</td>
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<tr>
<td></td>
<td>Shortness of breath and combined bone pain</td>
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<td>0.1 (NR)</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath and nosebleeds</td>
<td></td>
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<tr>
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<td>Shortness of breath and back pain</td>
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<td>Chest infection and chest pain</td>
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<td>Chest infection and nausea</td>
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<td>Shephard (2014)</td>
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<tr>
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<td>Non-calculable</td>
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</table>

**Abbreviations:** CI, confidence interval; FP, False positives; PPV, positive predictive value; TP, True positives, NR, Not reported. Shepard (2014) reports that PPVs were not calculated if < 5 cases had the feature(s) and CIs were omitted where < 10 cases or controls had the combined features.
Evidence statements:

The positive predictive values for myeloma of single symptoms presenting in a primary care setting ranged from 0% (for ‘acute low back pain’) to 0.7% (for hypercalcaemia in patients aged ≥ 60 years; 3 studies, N = 17798). The studies were subject to 1-3 bias or applicability concerns (See also Table 1).

The positive predictive values for myeloma of symptom pairs presenting in a primary care setting ranged from 0.1% (for raised creatinine with ‘shortness of breath’/ chest infection / joint pain, and for joint pain with ‘raised inflammatory markers’/back pain/ ‘combined bone pain’/ nausea/fracture/chest pain/ ‘shortness of breath’, and for ‘shortness of breath’ with chest infection / chest pain/ fracture/ nausea/ nosebleeds/ back pain/ weight loss, and for chest infection with nosebleeds/nausea, and for chest pain with weight loss; all in patients aged ≥ 60 years) to >10% (for hypercalcaemia with ‘back pain second episode’/ fracture / joint pain/rib pain, and for leucopenia with nosebleeds/fracture; all in patients aged ≥ 60 years; 1 study, N = 14860). The study was subject to 1 bias concern (see also Table 2).

Evidence tables

Deyo (1988)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
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<tr>
<td>A. risk of bias</td>
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<tr>
<td>Patient sampling</td>
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</tr>
<tr>
<td>Was a case-control design avoided?</td>
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<tr>
<td>Did the study avoid inappropriate exclusions?</td>
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<td>Could the selection of patients have introduced bias?</td>
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<table>
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<th>B. Concerns regarding applicability</th>
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<tbody>
<tr>
<td>Patient characteristics and setting</td>
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<tr>
<td>N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for &lt; 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%).</td>
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<td>Clinical setting:</td>
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INDEX TEST

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<td>Could the conduct or interpretation of the index test have introduced bias?</td>
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<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
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<tr>
<td><strong>REFERENCE STANDARD</strong></td>
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<td><strong>A. risk of bias</strong></td>
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<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
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<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
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<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
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<tr>
<td><strong>FLOW AND TIMING</strong></td>
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<td><strong>A. risk of bias</strong></td>
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<td>Was there an appropriate interval between index test and reference standard?</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
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<tr>
<td>Were all patients included in the analysis?</td>
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<tr>
<td>Could the patient flow have introduced bias?</td>
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<td><strong>NOTES</strong></td>
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</table>

Shephard (2014)
Patient sampling | Matched case-control study using patients in the UK’s Clinical Practice Research Database (CPRD).
---|---
Was a consecutive or random sample of patients enrolled? | No
Was a case-control design avoided? | No
Did the study avoid inappropriate exclusions? | Yes
For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders? | Yes
For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors? | Yes
Could the selection of patients have introduced bias? | High risk

B. Concerns regarding applicability

Patient characteristics and setting

| Cases: | N = 2703, 1449 males/ 1254 females, median age at diagnosis = 73 (IQR = 64-80) years; median number of consultations in the year before diagnosis = 16 (IQR = 10-25); UK. |
| Controls: | N = 12157; 6359 males/ 5798 females; median age at matched-case diagnosis = 73 (IQR = 65-80) years median number of consultations in the year before diagnosis = 8 (IQR = 4-14); UK. |

Inclusion criteria:
Cases: Patients aged ≥ 40 years with one of 23 myeloma diagnostic codes in the CPRD between January 2000 and December 2009, with min. 1 year of data before diagnosis. The first instance of a myeloma cancer code was assigned the data of diagnosis/index date.
Controls: Up to 5 controls per case, matched on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.

Exclusion criteria: Any case or control with less than 1 year of data before the index date; cases without controls; controls with myeloma; controls with only one line consisting of incomplete data (suggestion they had not sought medical care after registration).

Clinical setting: UK primary care

Are there concerns that the included patients and setting do not match the review question? | Low concern

INDEX TEST

A. Risk of bias

Index test

“Symptoms, diseases and abnormal investigations reported in the myeloma literature and from patient online support groups were studied”. “The GPRD contains over 100,000 medical codes; several codes can potentially be associated with each feature. A symptom library of codes was compiled for each feature. Occurrences of features were identified in the year before the index date. Only those features present in ≥2% of cases or controls were retained (this was invariably cases).” “Abnormal investigation results were defined as the patient having a test value falling outside their local laboratory’s normal range. Patients with a normal laboratory result were grouped with those who had not been tested.” “Some tests were grouped together. The raised inflammatory markers variable was a composite of any

Suspected Cancer: Appendix F (June 2015)
of abnormal erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein, as different local laboratories had local preferences for the inflammatory marker of choice; similarly abnormal liver function tests reflected a raised value of any of the hepatic enzymes reported by each laboratory. In clinical practice, haemoglobin, white cell count and platelets are normally requested together (‘the full blood count’). We used these slightly differently in our analyses; for the multivariable analyses, a composite variable ‘cytopenia’ was deemed to be positive if any of the haemoglobin, white cell count or platelets was abnormally low; for positive predictive values (see below) the three different cell types were analysed separately. Bone pain codes often had an anatomical descriptor as well as the words ‘bone pain’. We retained ‘rib pain’, ‘back pain’ and ‘joint pain’ as separate entities; remaining bone pain codes, such as ‘tibial pain’ were merged with the generic ‘bone pain’ code, making a group we called ‘combined bone pain’. “

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
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<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Investigators were kept ‘blind’ to other important confounding and prognostic factors?</td>
<td></td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>One of 23 myeloma diagnostic codes in the CPRD.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>A total of 16233 patients were identified, 13503 controls and 2730 cases. After the exclusion criteria were applied there were 12157 controls and 2703 cases.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>
**NOTES**

62 symptoms and 22 abnormal test results were considered initially.

**Suarez-Almazor (1997)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
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<tbody>
<tr>
<td>Patient sampling</td>
<td>Retrospective consecutive patient series</td>
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<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
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<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the study avoid inappropriate exclusions?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 1550, of whom N = 331 had chronic (> 3 months?) back pain, N = 963 had acute (< 3 months) low back pain, and N = 256 had back pain of unspecified duration. Of the patients with acute low back pain, 442 were males, and it appears that the mean (SD) age = 42.2 (15.6) years for the patients with acute low back pain, 14/963 had a history of cancer |
| Inclusion criteria: All patients aged ≥ 18 years presenting to four family clinics in Edmonton (Alberta, Canada) between January 1 1992 and December 31 1993 with low back pain or leg pain compatible with sciatic pain for which no visit had been made within the past 12 months. |
| Exclusion criteria: Low back pain attributable to visceral pain (e.g., urinary infection, inflammatory pelvic disease), previous diagnosis of ankylosing spondylitis, pregnancy. |
| Clinical setting: Four family clinics in Edmonton (Alberta, Canada), two of which are university-affiliated and hospital-based, with the other two based in the community. |

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
<td>Acute (&lt; 3 months) low back pain; not further specified.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Follow up consisting of chart review after a minimum of 2 years. Patients were considered to have cancer if recorded in the physician notes or in reports from laboratory or diagnostic tests.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
</tbody>
</table>
Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk
---|---

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern
---|---

FLOW AND TIMING

A. risk of bias

Flow and timing | The results are only presented for the patients with acute low back pain.
---|---
Was there an appropriate interval between index test and reference standard? | Yes
---|---
Did all patients receive the same reference standard? | Yes
---|---
Were all patients included in the analysis? | Yes
---|---
Could the patient flow have introduced bias? | Low risk
---|---

NOTES

13/963 patients with acute low back pain had active cancer. 3 of those 13 patients had the cancer diagnosis prior to the index visit; 3/13 patients had tumours that were probable causes of the acute low back pain (spinal infiltrates from multiple myeloma [2] and metastatic bone disease with compression fractures [1]), and 10/13 patients had cancer that was not considered to have caused the acute low back pain (bladder cancer [3], colon [1], breast [1], thyroid [1], lung [1], prostate [1], endometrium [1], oesophagus [1]). However, as it is not reported which of these patients already had a diagnosis of cancer pre-index visit, it is not possible to present the data accurately for the individual cancers.

References

Included studies


Excluded studies (with exclusion reason)


Exclusion reason : expert review


Exclusion reason : expert review

Exclusion reason: expert review


Exclusion reason: expert review


Exclusion reason: Narrative review


Exclusion reason: expert review


Exclusion reason: population not in PICO


Exclusion reason: population not in PICO


Exclusion reason: Not in PICO


Exclusion reason: population not in PICO


Exclusion reason: Not in PICO


Exclusion reason: population not in PICO


Exclusion reason: expert review


Exclusion reason: population not in PICO


Exclusion reason: case report


Exclusion reason: case report


Exclusion reason: Not in PICO


Exclusion reason: case report


Exclusion reason: case report


Exclusion reason: case report


Exclusion reason: population not in PICO


Exclusion reason: population not in PICO


Exclusion reason: Not in PICO


Exclusion reason: Narrative review


Exclusion reason: population not in PICO


Exclusion reason: expert review

Exclusion reason : expert review


Exclusion reason : cases only


Exclusion reason : case report


Exclusion reason : case report


Exclusion reason : expert review


Exclusion reason : population not in PICO


Exclusion reason : expert review


Exclusion reason : case report


Exclusion reason : Not in PICO


Exclusion reason : case report


Exclusion reason : case report


Exclusion reason : cases only


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Exclusion reason : case report

Exclusion reason : Narrative review

Exclusion reason : expert review

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Exclusion reason : case report


Exclusion reason : case report


Exclusion reason : expert review


Exclusion reason : population not in PICO


Exclusion reason : expert review


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Exclusion reason : case report


Exclusion reason : population not in PICO


Exclusion reason : population not in PICO


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Exclusion reason : Not in PICO


Exclusion reason : cases only
Review question:
Which investigations of symptoms of suspected myeloma should be done with clinical responsibility retained by primary care?

Results

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<td>11</td>
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<td>Embase</td>
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<td>636</td>
<td>54</td>
<td>08/04/2013</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>1980-2013</td>
<td>646</td>
<td>3</td>
<td>09/04/2013</td>
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<td>Psychinfo</td>
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<td>19/08/2014</td>
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</tbody>
</table>
Study results

No evidence was identified pertaining to the diagnostic accuracy of paraprotein/serum electrophoresis/Bence-Jones protein tests, ESR, X-ray, viscosity or calcium tests in patients with suspected myeloma cancer where the clinical responsibility was retained by primary care.

References

Included studies

None

Excluded studies (with excl reason)

   Exclusion reason : expert review
Exclusion reason : screening study


Exclusion reason : case report


Exclusion reason : expert review


Exclusion reason : repeat publication


Exclusion reason : population not in PICO


Exclusion reason : population not in PICO


Exclusion reason : population not in PICO


Exclusion reason : population not in PICO


Exclusion reason : Narrative review


Exclusion reason : population not in PICO


Exclusion reason : expert review


Exclusion reason : population not in PICO


Exclusion reason : Not in PICO
Exclusion reason : population not in PICO

Exclusion reason : cases only

Exclusion reason : Not in PICO

Exclusion reason : screening study

Exclusion reason : cases only

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Exclusion reason : population not in PICO

Exclusion reason : test not in PICO

Exclusion reason : population not in PICO

Exclusion reason : population not in PICO

Exclusion reason : test not in PICO

Exclusion reason : screening study

Exclusion reason : Not in PICO

Exclusion reason: population not in PICO

Exclusion reason: expert review

Exclusion reason: expert review

Exclusion reason: population not in PICO

Exclusion reason: population not in PICO

Exclusion reason: expert review

Exclusion reason: case report

Exclusion reason: population not in PICO

Exclusion reason: screening study

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Exclusion reason: test not in PICO

Exclusion reason: population not in PICO

Exclusion reason: population not in PICO

Ferrero, S., Capello, D., Svaldi, M., Boi, M., Gatti, D., Drandi, D., Rossi, D., Barbiero, S., Mantoan, B., Mantella, E., Zanni, M., Ghione, P., Larocca, A., Passera, R., Bertoni, F., Gattei, V., Forconi, F.,

Exclusion reason: test not in PICO


Exclusion reason: Narrative review


Exclusion reason: expert review


Exclusion reason: case report


Exclusion reason: case report


Exclusion reason: population not in PICO


Exclusion reason: case report


Exclusion reason: population not in PICO


Exclusion reason: population not in PICO


Exclusion reason: test not in PICO


Exclusion reason: not primary care


Exclusion reason: expert review

tyrosine phosphorylation of multiple cytosolic proteins and activation of Src-family kinases Fyn, Hck, and Lyn in multiple myeloma cell lines. Experimental Hematology, 25: 1367-1377.


Exclusion reason : test not in PICO


Exclusion reason : expert review


Exclusion reason : test not in PICO


Exclusion reason : test not in PICO


Exclusion reason : population not in PICO


Exclusion reason : not primary care


Exclusion reason : case report


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Exclusion reason : case report


Exclusion reason : expert review


Exclusion reason : test not in PICO


Exclusion reason : case report


Exclusion reason : expert review


Exclusion reason: case report


Exclusion reason: not primary care


Exclusion reason: population not in PICO


Exclusion reason: test not in PICO


Exclusion reason: population not in PICO


Exclusion reason: test not in PICO


Exclusion reason: test not in PICO


Exclusion reason: population not in PICO


Exclusion reason: population not in PICO


Exclusion reason: Not in PICO


Exclusion reason: test not in PICO


Exclusion reason: test not in PICO

Exclusion reason : test not in PICO


Exclusion reason : treatment study


Exclusion reason : expert review


Exclusion reason : test not in PICO


Exclusion reason : test not in PICO


Exclusion reason : case report


Exclusion reason : population not in PICO


Exclusion reason : test not in PICO


Exclusion reason : editorial


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Exclusion reason: not primary care

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Exclusion reason: cases only

Exclusion reason: screening study

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Exclusion reason: test not in PICO

Exclusion reason: test not in PICO

Exclusion reason: test not in PICO
Exclusion reason: test not in PICO

Exclusion reason: test not in PICO

Exclusion reason: population not in PICO
**NON-HODGKIN’S LYMPHOMA**

**Review question:**
What is the risk of Non-Hodgkin’s lymphoma in patients presenting in primary care with symptom(s)?

**Results**

**Literature search**

<table>
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<td>Premedline</td>
<td>All-2012</td>
<td>18</td>
<td>5</td>
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<td>Embase</td>
<td>All-2012</td>
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<td>1</td>
<td>16/10/12</td>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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Total References retrieved (after de-duplication): 256

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</table>

Total References retrieved (after de-duplication): 12
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

Study results
### Table 1: Non-Hodgkin’s lymphoma: Adult and mixed age populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyo (1988)</td>
<td>Back pain</td>
<td>All patients</td>
<td>0.1 (0.02-0.41) 2/1975 7 had other types of cancer: lymphoma (NOS): N = 2, unknown primary: N = 1, prostate: N = 1, retroperitoneal liposarcoma: N = 1, lung cancer: N = 1, renal cell: N = 1, multiple myeloma: N = 1, mucinous adenocarcinoma (of gallbladder?): N = 1</td>
</tr>
<tr>
<td>Williamson (1985)</td>
<td>Lymphadenopathy</td>
<td>All patients</td>
<td>0.8 (0.1-3.2) TP = 2, FP = 247 Cancer: Hodgkin’s: N = 1 Adenocarcinoma: N = 1</td>
</tr>
</tbody>
</table>

TP = True positives, FP = False positives.

### Table 2: Non-Hodgkin’s lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.53 (0.07-3.91)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.43 (0.06-3.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.35 (0.05-2.65)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.07 (0.03-0.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and</td>
<td>0.06 (0.04-0.11)</td>
</tr>
</tbody>
</table>
### Table 3: Non-Hodgkin’s lymphoma: Positive predictive values for teenage and young adult lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling head and neck</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling below neck excluding abdomen</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lymphadenopathy</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>‘Lump mass swelling head and neck’, ‘lymphadenopathy’ and ‘lump mass swelling’</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0903 (0.057-0.1425)</td>
</tr>
</tbody>
</table>

The positive predictive values are calculated using Bayesian statistics.
The positive predictive values are calculated using Bayesian statistics.

**Evidence statement(s):**

**Adult and mixed age populations**

Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin’s/Non-Hodgkin’s lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

**Children and teenagers and young adults**

The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 2-3).

**Evidence tables**

**Deyo (1988)**

<table>
<thead>
<tr>
<th><strong>PATIENT SELECTION</strong></th>
<th><strong>A. risk of bias</strong></th>
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<tbody>
<tr>
<td><strong>Patient sampling</strong></td>
<td>Prospective consecutive? patient series</td>
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<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Yes (probably)</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics and setting</strong></td>
</tr>
<tr>
<td>N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for &lt; 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%).</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong> Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint.</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Neck pain.</td>
</tr>
<tr>
<td><strong>Clinical setting:</strong> Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of</td>
</tr>
</tbody>
</table>
Are there concerns that the included patients and setting do not match the review question? | High concern

**INDEX TEST**

**A. Risk of bias**

Index test | Back pain; not further specified.

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes

**For diagnostic case-control studies:**

Investigators were kept 'blind' to other important confounding and prognostic factors? | Yes

Could the conduct or interpretation of the index test have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the included patients and setting do not match the review question? | Low concern

**REFERENCE STANDARD**

**A. Risk of bias**

Reference standard(s) | The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.

Is the reference standard likely to correctly classify the target condition? | Unclear

Were the reference standard results interpreted without knowledge of the results of the index tests? | No (but all patients had a positive index test)

Could the reference standard, its conduct, or its interpretation have introduced bias? | Unclear risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**FLOW AND TIMING**

**A. Risk of bias**

Flow and timing | All the patients are accounted for in the results.

Was there an appropriate interval between index test and reference standard? | Yes (probably)

Did all patients receive the same reference standard? | Yes

Were all patients included in the analysis? | Yes

Could the patient flow have introduced bias? | Low risk

**NOTES**

It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13
patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1) Dommett (2012; 2013a,b)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
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</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>High risk</td>
</tr>
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</table>

**B. Concerns regarding applicability**

**Cases:**
1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females.
Cancer type: Leukaemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132.
1064 teenagers and young adults (TYA): 15-24 years: Gender not reported.
Cancer type: Leukaemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17).

**Controls:**
15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females.
13206 TYA. Gender not reported

**Inclusion criteria:**
The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls.
Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.
Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed  
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. <em>No more information reported.</em></td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
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</table>
| *For diagnostic case-control studies:*  
Investigators were kept 'blind' to other important confounding and prognostic factors? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
<th></th>
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<tbody>
<tr>
<td><strong>Reference standard(s)</strong></td>
<td>Cancer diagnosis in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
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**FLOW AND TIMING**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Flow and timing</strong></td>
<td>All patients appear to be accounted for.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
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<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

This study is published in three papers.
### Williamson (1985)

#### PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
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<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Patient characteristics and setting

- N = 249, mean age = 24 years, 26% were < 15 years; 58% females.
- Inclusion criteria: Patients seen at the Family Medical Care Centre of the University of Missouri-Columbia, between July 1 19978 and June 30 1983 whose diagnoses were coded as “enlarged lymph nodes, not infected” (ICHPPC 266) and “lymphadenitis, acute” (ICHPPC 209).
- Exclusion criteria: None listed
- Clinical setting: Family Medical Care Centre of the University of Missouri-Columbia.

Are there concerns that the included patients and setting do not match the review question? | Low concern |

#### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

**Flow and timing**

11/249 patients did not fit the criteria for adequate follow up: 3/11 had return visits showing no increase in the size of the nodes, 6/11 had nodes < 1 cm in size and were told to come back if the nodes did not resolve, 2/11 presented with cervical lymph nodes described as 1 cm in size and follow up examination was not recommended. None of these 11 patients could be reached by phone.

**Was there an appropriate interval between index test and reference standard?** Yes (probably)

**Did all patients receive the same reference standard?** Yes

**Were all patients included in the analysis?** Unclear

**Could the patient flow have introduced bias?** Unclear risk

### NOTES

The author note that the study would not have included all the patients presenting with enlarged lymph nodes during the study period because not all such patients would have the diagnosis noted as required for study entry, e.g., a diagnosis of infectious mononucleosis made on the first visit would probably have been coded as such and not as enlarged lymph nodes.

### References

#### Included studies


#### Excluded studies (with excl reason)

  
  Excl reason: Discussion paper/not in PICO
  
  Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review/Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Retrospective case series of 80 patients based on case notes. Authors looked for cases of lymphadenopathy or acute lymphadenitis in the records. 19% of the cases were discovered by the physician (i.e., not patients consulting for this symptom). No aetiology recorded for 29% (N = 23) of the cases, and no cancers recorded as aetiology for the other 71%, but no clear verification of cause and final diagnoses not reported.

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO


Brockmeyer, N. and Barthel, B. Clinical manifestations and therapies of AIDS associated tumors. [Review] [244 refs]. European Journal of Medical Research 3[3], 127-147. 23-3-1998.
Excl reason: Narrative review
Excl reason: Narrative review
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Excl reason: Not in PICO
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Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO

Cholongitas, Evangelos, Papadakis, Emanouil, Kaklamanis, Loukas, and Dasenaki, Maria. Peripheral facial palsy in elderly: Not always a benign condition. [References]. *Geriatrics & Gerontology International* 9[1], 100-101. 2009.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Cuschiere, A. Malignant tumours of the stomach. [Review] [53 refs]. *Recenti Progressi in Medicina* 81[6], 374-386. 1990.
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative summary

Excl reason: Narrative review


Geh, J. I. and Spittle, M. F. Oncological problems in AIDS--a review of the clinical features and management. [Review] [74 refs]. Annals of the Academy of Medicine, Singapore 25[3], 380-391. 1996. Excl reason: Narrative review


Excl reason: Not in PICO (referred patients)
Groothoff, J. W. Long-term outcomes of children with end-stage renal disease. [Review] [30 refs].
Excl reason: Not in PICO
Excl reason: Not in PICO
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Excl reason: Not in PICO
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Excl reason: Not in PICO
Hanaoka, M., Tsukimori, K., Hojo, S., Abe, Y., Mutou, T., Muta, K., Iwasa, A., Yao, T., and Nakano, H. B-cell lymphoma during pregnancy associated with hemophagocytic syndrome and placental
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Narrative review
Excl reason: Not in PICO
Heitman, B. and Irizarry, A. Infectious disease causes of lymphadenopathy: localized versus diffuse. [Review] [50 refs]. Lippincott's Primary Care Practice 3[1], 19-38. 1999.
Excl reason: Narrative review
Hiller, E. [Malignant Hodgkin's and non-Hodgkin's lymphomas]. [German]. MMW Fortschritte der Medizin 147[9], 31-34. 3-3-2005.
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Excl reason: Narrative review


Kojima, M., Motoori, T., and Nakamura, S. Benign, atypical and malignant lymphoproliferative disorders in rheumatoid arthritis patients. [Review] [44 refs]. Biomedicine & Pharmacotherapy 60[10], 663-672. 2006. Excl reason: Narrative review


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Excl reason: Not in PICO

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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review/guideline

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Excl reason: Narrative review

Excl reason: Not in PICO

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Excl reason: Narrative review

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Excl reason: Narrative review

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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Munir, N. and Bradley, P. J. Diagnosis and management of neoplastic lesions of the submandibular triangle. Oral Oncology 44[3], 251-260. 2008.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Nakamura, S., Aoyagi, K., Iwanaga, S., Yao, T., Tsuneyoshi, M., and Fujishima, M. Synchronous and metachronous primary gastric lymphoma and adenocarcinoma: a clinicopathological study of 12
Excl reason: Not in PICO

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Excl reason: Narrative review

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Excl reason: Not in PICO

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Excl reason: Narrative review

Nuernberg, D. [Ultrasound of adrenal gland tumours and indications for fine needle biopsy (uFNB)]. [Review] [116 refs] [German]. Ultraschall in der Medizin 26[6], 458-469. 2005.
Excl reason: Narrative summary

Excl reason: Not in PICO
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Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Schleifenbaum, B. and Fehr, J. [Value of the blood picture and flow cytometry immunotyping in the early diagnosis of low-grade lymphoma]. [Review] [15 refs] [German]. Therapeutische Umschau 53[2], 117-122. 1996.
Excl reason: Narrative review

Excl reason: Published as abstract only. Not enough information available to ascertain relevance.

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

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Excl reason: Narrative review

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Excl reason: Narrative review
Teo, W.-Y., Chan, M.-Y., Ng, K.-C., and Tan, A.-M. Bony presentations of childhood haematological malignancy to the emergency room. Journal of Paediatrics and Child Health 48[4], 311-316. 2012.
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Tomiak, C. Prognosis of Primary Sjogren’s Syndrome with Special Regard to the Risk of Lymphoma. Aktuelle Rheumatologie 33[6], 325-336. 2008.
Excl reason: Narrative review

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Wierecky, J. and Bokemeyer, C. [Compression syndromes]. [Review] [28 refs] [German]. Internist 46[1], 9-18. 2005.
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Yamada, Y., Kamihira, S., Murata, K., Yamamura, M., Maeda, T., Tsukasaki, K., Jubash, T., Atogami, S., Sohda, H., Taguchi, T., and Tomonaga, M. Frequent hepatic involvement in adult T cell leukemia:
Excl reason: Not in PICO
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Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO/narrative review
Excl reason: Narrative review
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Not in PICO
Review question:
Which investigations of symptoms of suspected Non-Hodgkin’s lymphoma cancer should be done with clinical responsibility retained by primary care?

Results

Literature search

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Update Search

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Total References retrieved (after de-duplication): 22
Study results

No evidence was identified pertaining to the diagnostic accuracy of CT scan, ultrasound, chest X-ray or LDH in patients with suspected non-hodgkin's lymphoma cell cancer where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies
Excl reason: Not relevant to PICO
Excl reason: Single Case/Foreign Language
Excl reason: Population not relevant to PICO
Excl reason: Single Case/Foreign Language
Excl reason: Single Case


Excl reason: Not relevant to PICO

Excl reason: Expert Review

Excl reason: Single Case/Not relevant to PICO

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Excl reason: Expert Review

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Excl reason: Not in PICO

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Excl reason: Expert Review

Excl reason: Not relevant to PICO

Laryngoscope 93[10], 1276-1280. 1983.
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Excl reason: Single Case

Excl reason: Expert Review

Excl reason: Expert Review

Fey, M. F. [Salient clinical features of lymphoma and related lymphoproliferative disorders]. [German]. Therapeutische Umschau 67[10], 491-495. 2010.
Excl reason: Expert Review/Foreign Language

Excl reason: Single Case/Foreign Language

Excl reason: Not in PICO

Excl reason: Not relevant to PICO

Excl reason: Intervention not relevant to PICO

Excl reason: Single case

Excl reason: Interventions not relevant to PICO

Excl reason: Not in PICO

Excl reason: Expert Review

Goldschmidt, N., Libson, E., Bloom, A., Amir, G., and Paltiel, O. Clinical utility of computed tomography-guided core needle biopsy in the diagnostic re-evaluation of patients with
Excl reason: Not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Comparisons not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Single Case

Excl reason: Not in PICO

Excl reason: Not relevant to PICO

Excl reason: Not in PICO

Excl reason: Expert Review/Foreign Language

Excl reason: Not relevant to PICO/Foreign Language

Excl reason: Single Case

Excl reason: Not relevant to PICO
Ho, C. L. Clinical PET imaging--an Asian perspective. [Review] [53 refs]. Annals of the Academy of Medicine, Singapore 33[2], 155-165. 2004.
Excl reason: Expert Review
Excl reason: Not in PICO
Excl reason: Not in PICO
Excl reason: Expert Review
Excl reason: Single Case
Excl reason: Comparison not relevant to PICO
Excl reason: Not relevant to PICO
Excl reason: Not in PICO
Excl reason: Single Case
Excl reason: Not relevant to PICO
Excl reason: Expert Review
Excl reason: Not in PICO
Excl reason: Intervention not relevant to PICO
Excl reason: Not in PICO
Excl reason: Intervention not relevant to PICO/Foreign Language
Excl reason: Single Case
Excl reason: Not in PICO
Excl reason: Single Case/Foreign Language
Excl reason: Single Case/Foreign Language
Kirby, A. M. and Mikhaeel, N. G. The role of FDG PET in the management of lymphoma: what is the evidence base?. [Review] [123 refs]. *Nuclear Medicine Communications* 28[5], 335-354. 2007.
Excl reason: Expert Review
Excl reason: Not relevant to PICO
Excl reason: Expert Review
Excl reason: Not relevant to PICO
Excl reason: Intervention/Population not relevant to PICO
Excl reason: Intervention not relevant to PICO
Excl reason: Check relevance
Excl reason: Not in PICO
Excl reason: Single Case

Excl reason: Single Case/Foreign Language

Excl reason: Single Case

Excl reason: Single Case

Excl reason: Narrative review

Excl reason: Expert Review

Excl reason: Not relevant to PICO

Excl reason: Single Case

Excl reason: Single Case/Foreign Language

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Excl reason: Single Case

Excl reason: Not relevant to PICO

Excl reason: Single Case


Excl reason: Foreign Language/Not relevant to PICO

Excl reason: Single Case/Foreign Language

Excl reason: Single Case

Excl reason: Not relevant to PICO

Excl reason: Intervention not relevant to PICO

Excl reason: Comparison not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Foreign Language/Population not relevant

Excl reason: Not in PICO

Excl reason: Single Case

Excl reason: Not relevant to PICO


Excl reason: Not in PICO

Excl reason: Not relevant to PICO

Excl reason: Not relevant to PICO

Excl reason: Expert review

Excl reason: Not relevant to PICO

Excl reason: Expert Review

Excl reason: No data

Excl reason: Not relevant to PICO

Excl reason: Not in PICO

Excl reason: Expert Review/Foreign Language

Excl reason: Excl reason: Not relevant to PICO/Foreign Language

Excl reason: Expert Review

Excl reason: Single Case

Excl reason: Foreign Language
Excl reason: Not in PICO

Excl reason: Expert Review/Foreign Language
HODGKIN’S LYMPHOMA

Review question:
What is the risk of Hodgkin’s lymphoma in patients presenting in primary care with symptom(s)?

Results

Literature search

<table>
<thead>
<tr>
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<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
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<tbody>
<tr>
<td>Medline</td>
<td>All-2012</td>
<td>356</td>
<td>35</td>
<td>25/10/2012</td>
</tr>
<tr>
<td>Premedline</td>
<td>All-2012</td>
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<tr>
<td>Embase</td>
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<td>587</td>
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Total References retrieved (after de-duplication): 83

Update Search

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<tr>
<td>Premedline</td>
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<td>Embase</td>
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<td>Cochrane Library</td>
<td>10/2012-26/08/2014</td>
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<td>26/08/2014</td>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>10/2012-26/08/2014</td>
<td>42</td>
<td>0</td>
<td>26/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 0
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 2/3 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP, and that there was some uncertainty about the verification of the outcome for some of the patients. Dommett (2012; 2013a,b) employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

Study results

Table 1: Hodgkin’s lymphoma: Adult and mixed age populations
<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>PPVs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyo (1988)</td>
<td>Back pain</td>
<td>All patients</td>
<td>0.1 (0.02-0.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2/1975</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 had other types of cancer:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lymphoma (NOS): N = 2,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unknown primary: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prostate: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>retroperitoneal liposarcoma: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>lung cancer: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>renal cell: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multiple myeloma: N = 1,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mucinous adenocarcinoma (of gallbladder?): N = 1</td>
</tr>
<tr>
<td>Williamson (1985)</td>
<td>Lymphadenopathy</td>
<td>All patients</td>
<td>0.8 (0.1-3.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TP = 2, FP = 247</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cancer:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hodgkin’s: N = 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adenocarcinoma: N = 1</td>
</tr>
</tbody>
</table>

TP = True positives, FP = False positives.

Table 2: Hodgkin’s lymphoma: Positive predictive values for leukaemia/lymphoma childhood cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.53 (0.07-3.91)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.43 (0.06-3.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.35 (0.05-2.65)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.07 (0.03-0.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.06 (0.04-0.11)</td>
</tr>
</tbody>
</table>
Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.05 (0.02-0.13)

Bleeding 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.03 (0.01-0.08)

Pain 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.03 (0.01-0.06)

Musculoskeletal symptoms 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.02 (0.01-0.03)

Fever 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.01 (0.01-0.01)

Abdominal pain 0-3 months before diagnosis

All leukemia/lymphoma patients and controls aged 0-14 years

0.01(0-0.01)

≥ 3 consultations

All leukemia/lymphoma patients and controls aged 0-14 years

0.01(0.01-0.01)

The positive predictive values are calculated using Bayesian statistics.

Table 3: Hodgkin’s lymphoma: Positive predictive values for teenage and young adult lymphoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling head and neck</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.5034 (0.0696-3.68) Cases: 35/270 Controls: 1/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling below neck excluding abdomen</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0279 (0.0152-0.0515) Cases: 29/270 Controls: 15/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lymphadenopathy</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.278 (0.1-0.75) Cases: 77/270 Controls: 4/3350</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>‘Lump mass swelling head and neck’, ‘lymphadenopathy’ and ‘lump mass swelling below neck excluding abdomen’ combined as a single symptom</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0903 (0.057-0.1425)</td>
</tr>
</tbody>
</table>
The positive predictive values are calculated using Bayesian statistics.

**Evidence statement(s):**

**Adult and mixed age populations**
Back pain (1 study, N = 1975) and lymphadenopathy (1 study, N = 249) presenting in a primary care setting do not appear to confer a markedly increased risk of Hodgkin’s/Non-Hodgkin’s lymphoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

**Children and teenagers and young adults**
The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old, and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 2-3).

**Evidence tables**

**Deyo (1988)**

<table>
<thead>
<tr>
<th><strong>PATIENT SELECTION</strong></th>
<th><strong>A. risk of bias</strong></th>
<th><strong>Patient sampling</strong></th>
<th>Prospective consecutive? patient series</th>
<th>Unclear</th>
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</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Yes (probably)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Unclear risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%).** |

**Inclusion criteria:** Patients who sought treatment between March 1982 and September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint.

**Exclusion criteria:** Neck pain.

**Clinical setting:** Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.

| **Are there concerns that the included patients and setting do not match the review question?** | High concern |

**Dommett (2013b)**

<p>| ≥ 3 consultations | All lymphoma patients and controls aged 15-24 years | 0.0086 (0.0075-0.0099) Cases: 175/270 Controls: 294/3350 |</p>
<table>
<thead>
<tr>
<th>INDEX TEST</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>Back pain; not further specified.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
<td></td>
</tr>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REFERENCE STANDARD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reference standard(s)</strong></td>
<td>The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility.”</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
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<table>
<thead>
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<th>FLOW AND TIMING</th>
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</thead>
<tbody>
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<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All the patients are accounted for in the results.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

| NOTES | It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value. 38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer |
(1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder; 1)

Dommett (2012; 2013a,b)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
</tr>
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<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported |
| Inclusion criteria: The sample comprised all children and TYA aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently... |
registered on the date of diagnosis of their matched case (the index date).

Exclusion criteria: None listed
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.*

Were the index test results interpreted without knowledge of the results of the reference standard?  Yes

*For diagnostic case-control studies:*

Investigators were kept 'blind' to other important confounding and prognostic factors?  Yes

Could the conduct or interpretation of the index test have introduced bias?  Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question?  Low concern

**REFERENCE STANDARD**

**A. Risk of bias**

Reference standard(s)  Cancer diagnosis in the UK's General Practice Research Database.

Is the reference standard likely to correctly classify the target condition?  Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?  Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?  Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question?  Low concern

**FLOW AND TIMING**

**A. Risk of bias**

Flow and timing  All patients appear to be accounted for.

Was there an appropriate interval between index test and reference standard?  Yes

Did all patients receive the same reference standard?  Yes

Were all patients included in the analysis?  Yes

Could the patient flow have introduced bias?  Low risk

**NOTES**

This study is published in three papers.

Williamson (1985)
### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective consecutive patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

#### Patient characteristics and setting

| N = 249, mean age = 24 years, 26% were < 15 years; 58% females. |
| Inclusion criteria: Patients seen at the Family Medical Care Centre of the University of Missouri-Columbia, between July 1 19978 and June 30 1983 whose diagnoses were coded as “enlarged lymph nodes, not infected” (ICHPPC 266) and “lymphadenitis, acute” (ICHPPC 209). |
| Exclusion criteria: None listed |
| Clinical setting: Family Medical Care Centre of the University of Missouri-Columbia. |

Are there concerns that the included patients and setting do not match the review question? | Low concern |

#### INDEX TEST

**A. Risk of bias**

| Index test | Diagnoses coded as “enlarged lymph nodes, not infected” (ICHPPC 266) and “lymphadenitis, acute” (ICHPPC 209). |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

**A. Risk of bias**

| Reference standard(s) | Diagnoses were accepted if verified by history, physical examination or laboratory tests. Outcomes were determined, where possible, from the medical record. Follow up was considered adequate to determine an adverse outcome if one of four criteria were met: 1) A definite diagnosis was made, 2) The nodes were documented to be resolving, 3) There was at least one chart entry for any condition at least 6 months after the index visit for lymphadenopathy, or 4) The patient was reached by telephone and determined to have a favourable outcome. |
| Is the reference standard likely to correctly classify the target condition? | Yes |

| Were the reference standard results interpreted without knowledge of the results of the index tests? | No (but all patients had a positive index test) |

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined differ from the review question? | Low concern |
by the reference standard does not match the question?

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>11/249 patients did not fit the criteria for adequate follow up: 3/11 had return visits showing no increase in the size of the nodes, 6/11 had nodes &lt; 1 cm in size and were told to come back if the nodes did not resolve, 2/11 presented with cervical lymph nodes described as 1 cm in size and follow up examination was not recommended. None of these 11 patients could be reached by phone.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes (probably)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

The author note that the study would not have included all the patients presenting with enlarged lymph nodes during the study period because not all such patients would have the diagnosis noted as required for study entry, e.g., a diagnosis of infectious mononucleosis made on the first visit would probably have been coded as such and not as enlarged lymph nodes.

**References**

**Included studies**


**Excluded studies (with excl reason)**


Excl reason: Narrative review


Excl reason: Not in PICO


Excl reason: Not in PICO
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Bleyer, A. CAUTION! Consider Cancer: Common Symptoms and Signs for Early Detection of Cancer in Young Adults. Seminars in Oncology 36[3], 207-212. 2009.
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Case-control comparison of number of visits to GP for infectious & non-infectious diagnoses in 15 years prior to diagnosis, but omitted data in the year prior to diagnosis in order not to swamp earlier effects. Same data as Newton 2007
Damion, J. and Hybels, R. L. The neck mass. 2. Inflammatory and neoplastic causes. Postgraduate Medicine 81[6], 97-103. 106. Excl reason: Narrative review


Hiller, E. [Malignant Hodgkin’s and non-Hodgkin’s lymphomas]. [German]. MMW Fortschrritte der Medizin 147[9], 31-34. 3-3-2005.


Laskar, S., Gupta, T., Vimal, S., Muckaden, M. A., Saikia, T. K., Pai, S. K., Naresh, K. N., and Dinshaw, K. A. Consolidation radiation after complete remission in Hodgkin’s disease following six cycles of
<table>
<thead>
<tr>
<th>Title</th>
<th>Exclusion Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected Cancer: Appendix F (June 2015)</td>
<td></td>
</tr>
<tr>
<td>Newton, R., Crouch, S., Ansell, P., Simpson, J., Willett, E. V., Smith, A., Burton, C., Jack, A., and Roman, E. Hodgkin’s lymphoma and infection: findings from a UK case-control study. British Journal of Cancer 97[9], 1310-1314. 5-11-2007.</td>
<td>Case-control comparison of number of visits to GP for infectious &amp; non-infectious diagnoses in 15 years prior to diagnosis, but omitted data in the year prior to diagnosis in order not to swamp earlier effects. Same data as Crouch 2011. Only data included for the year prior to diagnosis was no of cases &amp; controls visiting their GP at least once split by infectious/non-infectious diagnosis (including tiredness &amp; malaise). No further split into individual symptoms.</td>
</tr>
</tbody>
</table>
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Published as abstract only, so not possible to check in more detail. May be published in full when update search done

Excl reason: Not in PICO

Excl reason: Not in PICO

Timms, J. M., Bell, A., Flavell, J. R., Murray, P. G., Rickinson, A. B., Traverse-Glehen, A., Berger, F., and Delecluse, H.-J. Target cells of Epstein-Barr-virus (EBV)-positive post-transplant
Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Narrative review

Excl reason: Not in PICO

White, L. N. Cancer prevention and detection: from twenty to sixty-five years of age. Oncology Nursing Forum 13[2], 59-64. 1986.
Excl reason: Narrative review

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

Excl reason: Not in PICO

**Review question:**

Which investigations of symptoms of suspected Hodgkin’s lymphoma should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>1980-2013</td>
<td>89</td>
<td>20</td>
<td>14/05/2013</td>
</tr>
</tbody>
</table>
Suspected Cancer: Appendix F (June 2015)

Study results

No evidence was identified pertaining to the diagnostic accuracy of chest x-ray, CT scan, ultrasound or LDH in patients with suspected Hodgkin’s lymphoma where the clinical responsibility was retained by primary care.

References

Included studies
None

Excluded studies (with excl reason)
Not in PICO

Narrative review

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO

Not in PICO


Not in PICO

Narrative review

Narrative review


Not in PICO
Not in PICO
Not in PICO
**SARCOMAS**

**BONE SARCOMA**

Review question:
What is the risk of bone sarcoma in patients presenting in primary care with symptom(s)?

Results

**Literature search**

<table>
<thead>
<tr>
<th>Database name</th>
<th>Dates Covered</th>
<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>All-2012</td>
<td>2069</td>
<td>78</td>
<td>11/10/12</td>
</tr>
<tr>
<td>Premedline</td>
<td>All-2012</td>
<td>57</td>
<td>8</td>
<td>11/10/12</td>
</tr>
<tr>
<td>Embase</td>
<td>All-2012</td>
<td>2009</td>
<td>76</td>
<td>11/10/12</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>All-2012</td>
<td>407</td>
<td>2</td>
<td>15/10/12</td>
</tr>
<tr>
<td>Psychinfo</td>
<td>All-2012</td>
<td>10</td>
<td>1</td>
<td>11/10/12</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>All-2012</td>
<td>706</td>
<td>14</td>
<td>15/10/12</td>
</tr>
<tr>
<td>Biomed Central</td>
<td>All-2012</td>
<td>138</td>
<td>5</td>
<td>15/10/12</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 155

**Update Search**

<table>
<thead>
<tr>
<th>Database name</th>
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<th>No of references found</th>
<th>No of references retrieved</th>
<th>Finish date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline</td>
<td>10/2012-26/08/2014</td>
<td>85</td>
<td>1</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Premedline</td>
<td>10/2012-26/08/2014</td>
<td>60</td>
<td>4</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Embase</td>
<td>10/2012-26/08/2014</td>
<td>258</td>
<td>6</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>10/2012-26/08/2014</td>
<td>262</td>
<td>0</td>
<td>26/08/2014</td>
</tr>
<tr>
<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
<td>10/2012-26/08/2014</td>
<td>134</td>
<td>0</td>
<td>26/08/2014</td>
</tr>
</tbody>
</table>

Total References retrieved (after de-duplication): 9
Risk of bias in the included studies

The risk of bias and applicability concerns are summarised per study in the figure below. The main issue to note is that 4/5 studies employed samples of patients that are not directly representative of an unselected symptomatic population of patients presenting to the UK-based GP. In the case of Pharisa (2009) whose sample consisted of patients presenting as emergencies, the symptom spectrum is likely to be of the more severe kind than those typically seen by a GP in the UK, but in the other cases (e.g., presentations to physiotherapists, chiropractors and hospital-based walk-in and family clinics) it is unclear how the patients differ from those of primary current interest. Dommett (2012, 2013a,b) only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence. Finally, two studies employed reference standards that are at some (unknown level of) risk of failing to identify all patients with cancer, which means that the relevant PPVs may be underestimated (to the extent that the reference standards have failed to identify patients with cancer).
### Study results

**Table 1: Bone sarcoma: Patients aged > 14-15 years**

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>PPVs (95% CI); prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyo (1988)</td>
<td>Back pain</td>
<td>All patients</td>
<td>0 (0-0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/1975</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None had bone sarcoma, but N = 9 had other types of cancer</td>
</tr>
<tr>
<td>Suarez-Almazor (1997)</td>
<td>Acute low back pain</td>
<td>All patients</td>
<td>TP = 0-1, FP = 962-963</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unclear if diagnosis prior to symptom</td>
</tr>
<tr>
<td>Henschke (2009)</td>
<td>Acute low back pain</td>
<td>All patients</td>
<td>0 (0-0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/1172</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None had cancer</td>
</tr>
<tr>
<td>Henschke (2009)</td>
<td>Acute low back pain + age at onset &lt; 20 years or &gt; 55 years</td>
<td>Subgroup with both symptoms</td>
<td>0 (0-1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/281</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None had cancer</td>
</tr>
<tr>
<td>Henschke (2009)</td>
<td>Acute low back pain + previous history of cancer</td>
<td>Subgroup with both symptoms</td>
<td>0 (0-9.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None had cancer</td>
</tr>
<tr>
<td>Henschke (2009)</td>
<td>Acute low back pain + tried bed rest, but no relief</td>
<td>Subgroup with both symptoms</td>
<td>0 (0-2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/192</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None had cancer</td>
</tr>
<tr>
<td>Henschke (2009)</td>
<td>Acute low back pain + unexplained weight loss</td>
<td>Subgroup with both symptoms</td>
<td>0 (0-69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/3</td>
</tr>
</tbody>
</table>
None had cancer

Henschke (2009) Acute low back pain +
insidious onset Subgroup with both
symptoms 0 (0-2.3)
0/202
None had cancer

Henschke (2009) Acute low back pain +
systemically unwell Subgroup with both
symptoms 0 (0-15.5)
0/27
None had cancer

Henschke (2009) Acute low back pain +
constant progressive
non-mechanical pain Subgroup with both
symptoms 0 (0-13)
0/33
None had cancer

Henschke (2009) Acute low back pain +
sensory level altered
from trunk down Subgroup with both
symptoms 0 (0-20.9)
0/19
None had cancer

TP = True positives, FP = False positives.

Table 2: Bone sarcoma: Positive predictive values for child- or young adulthood bone tumour/soft
tissue sarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.14)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Trauma 0-3 months before diagnosis</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 15-24 years</td>
<td>0.0415 (0.0124-0.1392)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases: 19/196</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls: 3/2438</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Musculoskeletal symptoms</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 15</td>
<td>0.0093 (0.0058-0.0151)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases: 37/196</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls: 26/2438</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Chest pain</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 15</td>
<td>0.0027 (0.001-0.0077)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases: 5/196</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls: 12/2438</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>≥ 3 consultations</td>
<td>All bone tumour/soft tissue sarcoma patients and controls aged 15</td>
<td>0.003 (0.0024-0.0037)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases: 86/196</td>
</tr>
</tbody>
</table>
The positive predictive values are calculated using Bayesian statistics. TP = true positives, FP = false positives

**Evidence statement(s):**

**Adult patients**
Acute low back pain alone (2 studies, N = 2135) or in combination with other single risk factors/symptoms (1 study, N = 19-281), and back pain (1 study, N = 1975) presenting in a primary care setting do not appear to confer an increased risk of bone sarcoma, although the study populations are probably not directly representative of the typical unselected symptomatic UK GP population (see also Table 1).

**Children, teenage and young adult patients**
The positive predictive values of having childhood or young adulthood bone sarcoma tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for ‘lump mass swelling below neck excluding abdomen’) for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 2).

Neck pain (1 study, N = 170) presenting in a primary care setting does not appear to confer an increased risk of bone sarcoma, although the study population is not directly representative of the typical unselected symptomatic UK GP population (see also Table 2).

**Evidence tables**

**Deyo (1988)**

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
</tr>
</tbody>
</table>

| **B. Concerns regarding applicability** |
| Patient characteristics and setting | N = 1975, mean (SD; range) age = 39.5 (15.4; 15-86) years, 62% females. 54% of the patients were seeking medical care for back pain for the first time and 76% of the patients had had back pain for < 3 months. 3% had a history of back pain surgery. Maximal back pain in the low back (84%) or in the upper back (16%). Inclusion criteria: Patients who sought treatment between March 1982 and |

<table>
<thead>
<tr>
<th>Pharisa (2009)</th>
<th>Neck pain</th>
<th>Children ≤ 16 years</th>
<th>Controls: 189/2438</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (0-2.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/ 170</td>
</tr>
</tbody>
</table>
September 1984 in the walk-in clinic of a public hospital where virtually all patients are self-referred. In each case back pain was part of the chief complaint.
Exclusion criteria: Neck pain.
Clinical setting: Walk-in clinic of a public hospital; this clinic is a source of primary care for indigent persons in a county in the USA with a population of approximately 1 million.

| Are there concerns that the included patients and setting do not match the review question? | High concern |
| **INDEX TEST** |  |
| **A. Risk of bias** |  |
| Index test | Back pain; not further specified. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| **REFERENCE STANDARD** |  |
| **A. risk of bias** |  |
| Reference standard(s) | The reference standard consisted of a search on each patient name in the institutional tumour registry ≥ 6 months after the index visit. The registry included every patient with a histological diagnosis of cancer made in the authors’ hospital system regardless of site of care. The authors point out that “while this method might fail to identify cancer patients who sought care elsewhere, it is likely that most patients sought follow-up for a particular illness at the same facility. |
| Is the reference standard likely to correctly classify the target condition? | Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | No (but all patients had a positive index test) |
| **B. Concerns regarding applicability** |  |
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |
| **FLOW AND TIMING** |  |
| **A. risk of bias** |  |
| Flow and timing | All the patients are accounted for in the results. |
| Was there an appropriate interval between index test and reference standard? | Yes (probably) |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
Could the patient flow have introduced bias? | Low risk
--- | ---
**NOTES**
It is a concern that some patients with cancer might have been missed due to the choice of reference standard because this would result in an underestimation of the positive predictive value.
38/1975 patients were found in the tumour registry. Of those 38, 13 patients had tumours that were probable causes of back pain, and 4 of these 13 patients already had a diagnosis of cancer at presentation. The 9/1975 patients who had undiagnosed cancer that the back pain could be attributed to had: Lymphoma (NOS; 2), cancer of unknown primary (1), prostate cancer (1), retroperitoneal liposarcoma (1), lung cancer (1), renal cell (1), multiple myeloma (1), mucinous adenocarcinoma (of gallbladder?; 1)

Dommett (2012; 2013a,b)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

For diagnostic case-control studies:

- Attempts were made within the design or analysis to balance the comparison groups for potential confounders? | Yes |
- The groups were comparable at baseline, including all major confounding and prognostic factors? | Yes |

**Could the selection of patients have introduced bias?** | High risk

**B. Concerns regarding applicability**

| Patient characteristics and setting | Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported |
| Inclusion criteria: The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index
Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.

Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date).

Exclusion criteria: None listed

Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

**Index test**
The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. No more information reported.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

For diagnostic case-control studies:
Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
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</thead>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Cancer diagnosis in the UK’s General Practice Research Database.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
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<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
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#### B. Concerns regarding applicability

<table>
<thead>
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<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
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</table>

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th>Flow and timing</th>
<th>All patients appear to be accounted for.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Index Test</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>An episode of acute low back pain was defined as pain in the area bounded superiorly by T12 and inferiorly by the buttock crease, lasting for more than 24 hours but less than 6 weeks, and preceded by a period of at least 1 month without back pain. Patients remained eligible if they also had pain that referred beyond this region.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**PATIENT SELECTION**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive patient series</th>
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</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 1172, mean (SD) age = 43.97 (15.1) years, 626 males/546 females; Primary care physician consulted: Medical practitioner (N = 267), physiotherapist (N = 851), chiropractor (N = 54); Previous episode of low back pain (N = 888); Duration of low back pain: < 1 week (N = 696), 1-2 weeks (N = 145), 2-3 weeks (N = 174), 3-4 weeks (N = 173), 4-5 weeks (N = 30), 5-6 weeks (N = 54). |

**Inclusion criteria**: Consecutive English-speaking (and writing) patients aged ≥ 14 years with acute low back pain who presented for a first consultation to participating primary care providers in the Sydney region of Australia. Please note that in Australia, the majority of primary care management for low back pain is provided by general medical practitioners, physiotherapists and chiropractors.

**Exclusion criteria**: Diagnosis of serious pathology prior to the consultation, which was considered to be the cause of the current episode of low back pain.

**Clinical setting**: Primary care (including physiotherapy and chiropractic)

Are there concerns that the included patients and setting do not match the review question? High concern

**NOTES**

This study is published in three papers.
### Interpretation differ from the review question?

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>The reference standard consisted of close follow up for 12 months. Participants were contacted by telephone 6 weeks, 3 months, and 12 months after the initial consultation. At each follow up contact, participants were asked the following question: “Low back pain is occasionally the result of a fracture, infection, arthritis, or cancer. Has a health care provider said that your back pain is caused by one of these rare diseases?” Participants were also prompted to provide any further details of a diagnosis or explanation for their low back pain that had been provided to them. All patients with potentially serious pathology were subsequently examined by a study rheumatologist. At each follow up contact, participants were also questioned to establish whether they had recovered from the episode of low back pain. Recovery was defined as 1 month with no pain, no interference with function due to pain, and return to previous work status for 1 month. Patients suspected by their primary care clinician of having a serious spinal pathology and those who reported having a serious spinal pathology during the follow up period were referred immediately to 1 of 2 study rheumatologists for a clinical assessment. Within 2 weeks from the time of referral, the rheumatologists examined each patient in their clinics and were additionally provided with the complete medical histories and all test results.</th>
</tr>
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<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for in the results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
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<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Please note that the primary care physician consulted were: Medical practitioner: N = 267, physiotherapist: N = 851, chiropractor: N = 54

**Pharisa (2009)**

**PATIENT SELECTION**

**A. risk of bias**

| Patient sampling | Retrospective consecutive patient series |
Was a consecutive or random sample of patients enrolled? | Yes
---|---
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Low risk

B. Concerns regarding applicability

Patient characteristics and setting | N = 170 (61 females/109 males), mean age = 9.05 years, median age = 9 years (range = 7 weeks to 16 years). A history of trauma was clearly reported in 106 of the children and clinical examination revealed restricted neck movements in 48 of these patients and painful movements without restriction in 28 of these patients. None of the patients had a neurological deficit on initial physical examination.

Inclusion criteria: All children aged ≤ 16 years presenting with neck pain and/or restricted neck movements from October 2004 to September 2005. Although any child with a complaint of neck pain was considered for inclusion in the study, only those whose neck pain was confirmed during medical examination were included.

Exclusion criteria: Toxic-appearing children with obvious signs of meningitis

Clinical setting: Emergency department of the Children’s Hospital of Lausanne, Switzerland

Are there concerns that the included patients and setting do not match the review question? | High concern

INDEX TEST

A. Risk of bias

Index test | “Neck pain confirmed during medical examination”

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes
Could the conduct or interpretation of the index test have introduced bias? | Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

REFERENCE STANDARD

A. Risk of bias

Reference standard(s) | Chart review and follow-up, including telephone calls to paediatricians to confirm final diagnosis

Is the reference standard likely to correctly classify the target condition? | Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? | No (but all patients had a positive index test)

Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern

FLOW AND TIMING

A. risk of bias
Follow up data were obtained by telephone in 134/170 patients, but final diagnoses are presented for all 170 patients.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Suarez-Almazor (1997)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective consecutive patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
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</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1550, of whom N = 331 had chronic (&gt; 3 months?) back pain, N = 963 had acute (&lt; 3 months) low back pain, and N = 256 had back pain of unspecified duration. Of the patients with acute low back pain, 442 were males, and it appears that the mean (SD) age = 42.2 (15.6) years for the patients with acute low back pain, 14/963 had a history of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>All patients aged ≥ 18 years presenting to four family clinics in Edmonton (Alberta, Canada) between January 1 1992 and December 31 1993 with low back pain or leg pain compatible with sciatic pain for which no visit had been made within the past 12 months.</td>
</tr>
<tr>
<td>Exclusion criteria:</td>
<td>Low back pain attributable to visceral pain (e.g., urinary infection, inflammatory pelvic disease), previous diagnosis of ankylosing spondylitis, pregnancy.</td>
</tr>
<tr>
<td>Clinical setting:</td>
<td>Four family clinics in Edmonton (Alberta, Canada), two of which are university-affiliated and hospital-based, with the other two based in the community.</td>
</tr>
</tbody>
</table>

Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Acute (&lt; 3 months) low back pain; not further specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
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<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**
A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Follow up consisting of chart review after a minimum of 2 years. Patients were considered to have cancer if recorded in the physician notes or in reports from laboratory or diagnostic tests.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING

A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>The results are only presented for the patients with acute low back pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

13/963 patients with acute low back pain had active cancer. 3 of those 13 patients had the cancer diagnosis prior to the index visit; 3/13 patients had tumours that were probable causes of the acute low back pain (spinal infiltrates from multiple myeloma [2] and metastatic bone disease with compression fractures [1]), and 10/13 patients had cancer that was not considered to have caused the acute low back pain (bladder cancer [3], colon [1], breast [1], thyroid [1], lung [1], prostate [1], endometrium [1], oesophagus [1]). However, as it is not reported which of these patients already had a diagnosis of cancer pre-index visit, it is not possible to present the data accurately for the individual cancers.

References

Included studies


**Excluded studies (with excl reason)**


Guideline


Patient information material


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


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Narrative review


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Narrative review

Systematic review, included studies checked for relevance.
Not in PICO

Narrative review

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Narrative review

Russian. Narrative review?

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Narrative review

Not in PICO; found in the van Hoogen review

Adolescent Medicine State of the Art Reviews, 10: 419-435.
Narrative review
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Not in PICO


Narrative review


Narrative review


Review, not systematic, but checked references and ordered an additional 2.


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**Review question:**
Which investigations of symptoms of suspected bone sarcoma should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

<table>
<thead>
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<th>Database name</th>
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<td>104</td>
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<td>Web of Science (SCI &amp; SSCI) and ISI Proceedings</td>
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Total References retrieved (after de-duplication): 219
**Update Search**

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</table>

Total References retrieved (after de-duplication): 19

**Study results**

No evidence was identified pertaining to the diagnostic accuracy of x-ray, calcium or alkaline phosphatase in patients with suspected bone sarcoma where the clinical responsibility was retained by primary care.

**References**

**Included studies**

None

**Excluded studies (with excl reason)**


Not in PICO


Not in PICO

Narrative review

Narrative review

Not in PICO

Guideline

Not in PICO

Not in PICO

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Narrative review


Narrative review


Not in PICO


Not in PICO


Not in PICO

Related Research, 28-33.

Not in PICO


Narrative review


Not in PICO


Narrative review


Systematic review, included studies checked for relevance.


Not in PICO


Narrative review


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Narrative review

<table>
<thead>
<tr>
<th>Title</th>
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<tbody>
<tr>
<td>Loening, S. A. &amp; Schnorr, D.</td>
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<tr>
<td>Kabukcuoglu, F., Kabukcuoglu, Y., Kuzgun, U. &amp; Evren, I.</td>
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**Internal Medicine, 16: 14-23.**

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Not in PICO
In Russian. Not enough information can be extracted to ascertain relevance
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Narrative review
Duplicate
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Narrative review
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Narrative review

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Langenbecks Archiv fur Chirurgie, Supplement.: 410-414.
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SOFT TISSUE SARCOMA

Review question:
What is the risk of soft tissue sarcoma in patients presenting in primary care with symptom(s)?

Results

Literature search

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Risk of bias in the included studies

The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study only presented results for bone and soft tissue sarcoma in combination and also employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting the influence of the latter.

---

Study results

Table 1: Soft tissue sarcoma: Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma

<table>
<thead>
<tr>
<th>Study</th>
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<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
<th>Frequency</th>
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<td>Lump mass swelling below neck excluding</td>
<td>All bone cancer tumour/soft tissue</td>
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<tr>
<td>Symptoms / Events</td>
<td>Patients and Controls</td>
<td>Evidence Statement(s)</td>
<td>Evidence Tables</td>
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<td>--------------------------------------------------------</td>
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<tr>
<td>abdomen 0-3 months before diagnosis</td>
<td>sarcoma patients and controls aged 0-14 years</td>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
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<tr>
<td>Trauma 0-3 months before diagnosis</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
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<td>Lump mass swelling</td>
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</table>

The positive predictive values are calculated using Bayesian statistics.

**Evidence statement(s):**

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for 'lump mass swelling below neck excluding abdomen') for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for 'lump mass swelling') for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 1).

**Evidence tables**

Dommett (2012; 2013a,b)
### PATIENT SELECTION

#### A. risk of bias

<table>
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<th>Patient sampling</th>
<th>Population-based nested case-control study using data from the General Practice Research Database (GPRD)</th>
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<tr>
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<td>No</td>
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<td>Did the study avoid inappropriate exclusions?</td>
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<td><strong>For diagnostic case-control studies:</strong> Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
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<tr>
<td><strong>For diagnostic case-control studies:</strong> The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
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<td>Could the selection of patients have introduced bias?</td>
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#### B. Concerns regarding applicability

| Patient characteristics and setting | Cases: 1267 children; aged 0-4 years: N = 436; aged 5-14 years: N = 831; 703 males/564 females. Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132. 1064 teenagers and young adults (TYA): 15-24 years: Gender not reported. Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17). Controls: 15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females. 13206 TYA. Gender not reported |
| Inclusion criteria: | The sample comprised all children and TYA aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls. Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used. Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date). Exclusion criteria: None listed Clinical setting: Primary care, UK. |

Are there concerns that the included patients and setting | Low concern |
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<td><strong>Index test</strong></td>
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</table>
The GPRD uses just over 100,000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. *No more information reported.* |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors? | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |
| **B. Concerns regarding applicability** |  |
| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |
| **REFERENCE STANDARD** |  |
| **A. Risk of bias** |  |
| Reference standard(s) | Cancer diagnosis in the UK’s General Practice Research Database. |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |
| **B. Concerns regarding applicability** |  |
| Are there concerns that the target condition as defined by the reference standard does not match the review question? | Low concern |
| **FLOW AND TIMING** |  |
| **A. Risk of bias** |  |
| Flow and timing | All patients appear to be accounted for. |
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| **Could the patient flow have introduced bias?** | Low risk |
| **NOTES** |  
This study is published in three papers. |

**References**

**Included studies**


Excluded studies (with excl reason)


Narrative review

Not in PICO


Narrative review


Guideline


Not in PICO


Narrative review


Narrative review


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Narrative review


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Narrative review


Abstract: (from the chapter) present basic medical information about childhood cancer / [present] an overview of the characteristics, manifestations, and current thought regarding etiology / [present] information about establishing and explaining the diagnosis and treatment plans to the family / [discuss] the course and general principles of cancer treatment / [discuss] the most common pediatric malignancies [e.g., acute lymphoblastic and nonlymphoblastic leukemia, brain tumors, lymphomas, Wilms' tumor, neuroblastoma, bone tumors and soft tissue sarcomas, and retinoblastoma] / [summarize the] late effects of treatment (PsycINFO Database Record (c) 2012 APA, all rights reserved)


Abstract: (from the chapter) Bone and soft tissue sarcomas are a heterogeneous group of cancers that arise from primitive mesenchymal cells throughout the body. Population-based data suggest that these cancers account for approximately 0.9% of cancer cases overall, but 13% of cancers in pediatric patients. Aggressive multimodality therapy, including various combinations of surgery, chemotherapy, and radiotherapy, is generally necessary for cure. Currently, the overall 5-year survival rate of patients with bone and soft tissue sarcomas is about two-thirds of that of the general population. Thus, sarcomas produce considerable morbidity as well as mortality. This chapter reviews the major clinical features, treatment, and outcomes of bone and soft tissue sarcomas, and addresses the major psychological issues facing individuals affected by these rare tumors. (PsycINFO Database Record (c) 2012 APA, all rights reserved)


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**Review question:**
Which investigations of symptoms of suspected soft tissue sarcoma should be done with clinical responsibility retained by primary care?

**Results**

**Literature search**

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Study results

No evidence was identified pertaining to the diagnostic accuracy of ultrasound in patients with suspected soft tissue sarcoma where the clinical responsibility was retained by primary care.

References

Included studies

None

Excluded studies (with excl reason)


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Narrative review
CHILDHOOD CANCERS

NEUROBLASTOMA, RETINOBLASTOMA, WILM’S TUMOUR

Review question:
What is the risk of neuroblastoma, retinoblastoma and Wilm’s tumour in children presenting in primary care with symptom(s)?

Results

Literature search

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### Wilm’s tumour: Update Search

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Risk of bias in the included studies
The risk of bias and applicability concerns are summarised for the included study in the figure below. The main issue to note is that the study employed a case-control design which has been shown to inflate the test accuracy characteristics. However, the statistical analyses employed by the authors may have gone some way in counteracting this influence.

Study results
Table 1: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for any childhood cancer: Patients aged 0-14 years

<table>
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<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
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<td>Dommett (2012)</td>
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<td>All patients</td>
<td>0.055 (0.047-0.065) Cases: 342/1267 Control: 211/15318</td>
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<td>All patients</td>
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<td>Back pain</td>
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<td>Dommett (2013a)</td>
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<td>Cases: 49/1267</td>
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<tr>
<td>Dommett (2012)</td>
<td>Lymphadenopathy 0-12 months before diagnosis</td>
<td>Patients aged 0-4 years</td>
<td>0.135 (0.055-0.335)</td>
</tr>
<tr>
<td>Dommett (2012)</td>
<td>Lump/mass/swelling 0-12 months before diagnosis</td>
<td>Patients aged 0-4 years</td>
<td>0.198 (0.099-0.399)</td>
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</table>

The positive predictive values are calculated using Bayesian statistics.

Table 2: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for any childhood cancer: Patients aged 0-4 years
### Table 3: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for any childhood cancer: Patients aged 5-14 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
<th>Frequency</th>
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<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-3 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.056 (0.047-0.068)</td>
<td>Cases: 246/831 Control: 156/10516</td>
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<tr>
<td>Dommett (2012)</td>
<td>Any NICE alert symptom 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.075 (0.066-0.084)</td>
<td>Cases: 303/831 Control: 581/10561</td>
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<tr>
<td>Dommett (2012)</td>
<td>Neurological symptoms 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.091 (0.067-0.123)</td>
<td>Cases: 65/831 Control: 102/10516</td>
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<td>Dommett (2012)</td>
<td>Headache 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.055 (0.043-0.07)</td>
<td>Cases: 82/831 Control: 213/10516</td>
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<td>Dommett (2012)</td>
<td>Lymphadenopathy 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.118 (0.085-0.164)</td>
<td>Cases: 62/831 Control: 75/10516</td>
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<tr>
<td>Dommett (2012)</td>
<td>Lump/mass/swelling 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.154 (0.099-0.24)</td>
<td>Cases: 40/831 Control: 37/10516</td>
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<td>Fatigue 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.082 (0.053-0.125)</td>
<td>Cases: 32/831 Control: 56/10516</td>
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<td>Dommett (2012)</td>
<td>Back pain 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.075 (0.05-0.111)</td>
<td>Cases: 36/831 Control: 69/10516</td>
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<td>Bruising 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.049 (0.029-0.084)</td>
<td>Cases: 18/831 Control: 52/10516</td>
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</table>

The positive predictive values are calculated using Bayesian statistics.
The positive predictive values are calculated using Bayesian statistics.

Table 4: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for leukaemia/lymphoma childhood cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
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<th>Positive predictive value (95% CI)</th>
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<td>Dommett (2012)</td>
<td>Urinary symptoms 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>0.143 (0.05-0.407) Cases: 7/831 Control: 7/10516</td>
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<tr>
<td>Dommett (2012)</td>
<td>Hepatosplenomegaly 0-12 months before diagnosis</td>
<td>Patients aged 5-14 years</td>
<td>Cases: 7/831 Control: 0/10516</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Bruising 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.53 (0.07-3.91)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pallor 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.43 (0.06-3.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling head and neck 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.35 (0.05-2.65)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Fatigue 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.07 (0.03-0.15)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lymphadenopathy 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.06 (0.04-0.11)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.05 (0.02-0.13)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Bleeding 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.08)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.02 (0.01-0.03)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Fever 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0.01-0.01)</td>
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</table>
The positive predictive values are calculated using Bayesian statistics.

Table 5: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for teenage and young adult leukaemia

<table>
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<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI)</th>
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</thead>
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<td>Abdominal pain 0-3 months before diagnosis</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All leukemia/lymphoma patients and controls aged 0-14 years</td>
<td>0.01 (0.01-0.01)</td>
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</table>

The positive predictive values are calculated using Bayesian statistics.

Table 6: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for teenage and young adult lymphoma

<table>
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<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
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<td>Dommett (2013b)</td>
<td>Lump mass swelling head and neck</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.5034 (0.0696-3.68)</td>
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<td>Cases: 35/270 Controls: 1/3350</td>
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<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling below neck excluding abdomen</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0279 (0.0152-0.0515)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases: 29/270 Controls: 15/3350</td>
<td></td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Lymphadenopathy</td>
<td>All lymphoma patients and controls aged 15-24 years</td>
<td>0.0903 (0.057-0.1425)</td>
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<tr>
<td></td>
<td></td>
<td>Cases: 77/270 Controls: 4/3350</td>
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Suspected Cancer: Appendix F (June 2015)


The positive predictive values are calculated using Bayesian statistics.

Table 7: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for central nervous system (CNS) child- or young adulthood cancer tumour

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
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</thead>
<tbody>
<tr>
<td>Dommett (2013a)</td>
<td>Abnormal movement 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.11 (0.03-0.35)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Visual symptoms 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.07 (0.02-0.24)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Vomiting 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.04 (0.02-0.07)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Headache 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.03 (0.02-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Pain 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.08)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Seizure 0-3 months before diagnosis</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.02 (0.01-0.06)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All CNS childhood cancer tumour patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
</tr>
<tr>
<td>Dommett (2013b)</td>
<td>Seizure</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0238 (0.0082-0.0695) Cases: 18/154 Controls: 4/1906</td>
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<tr>
<td>Dommett (2013b)</td>
<td>Headache</td>
<td>All CNS patients and controls aged 15-24 years</td>
<td>0.0145 (0.0077-0.0276) Cases: 33/154 Controls: 12/1906</td>
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### Table 8: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for child- or young adulthood bone cancer tumour/soft tissue sarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
<th>Patient group</th>
<th>Positive predictive value (95% CI) Frequency</th>
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<tr>
<td>Dommett (2013a)</td>
<td>Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.14)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0.01 (0-0.01)</td>
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<tr>
<td>Dommett (2013a)</td>
<td>Trauma 0-3 months before diagnosis</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
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<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 0-14 years</td>
<td>0 (0-0)</td>
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<tr>
<td>Dommett (2013b)</td>
<td>Lump mass swelling</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years</td>
<td>0.0415 (0.0124-0.1392)</td>
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<td>Dommett (2013b)</td>
<td>Musculoskeletal symptoms</td>
<td>All bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years</td>
<td>0.0093 (0.0058-0.0151)</td>
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</table>

The positive predictive values are calculated using Bayesian statistics.
controls aged 15-24 years  Controls: 26/2438

Dommett (2013b)  Chest pain  All bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years  0.0027 (0.001-0.0077)  Cases: 5/196  Controls: 12/2438

Dommett (2013b)  ≥ 3 consultations  All bone cancer tumour/soft tissue sarcoma patients and controls aged 15-24 years  0.003 (0.0024-0.0037)  Cases: 86/196  Controls: 189/2438

The positive predictive values are calculated using Bayesian statistics.

Table 9: Childhood cancers (neuroblastoma, retinoblastoma, Wilm’s tumour): Positive predictive values for childhood abdominal cancer tumour

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptom(s)</th>
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<tr>
<td>Dommett (2013a)</td>
<td>Bleeding 0-3 months before diagnosis</td>
<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0.03 (0.01-0.12)</td>
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<td>Lump mass swelling below neck excluding abdomen 0-3 months before diagnosis</td>
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<td>Dommett (2013a)</td>
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<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0.02 (0.00-0.1)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Abdominal pain 0-3 months before diagnosis</td>
<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0.01 (0.01-0.02)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Musculoskeletal symptoms 0-3 months before diagnosis</td>
<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0.01 (0.00-0.01)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>Childhood infection 0-3 months before diagnosis</td>
<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Dommett (2013a)</td>
<td>≥ 3 consultations</td>
<td>All abdominal cancer patients and controls aged 0-14 years</td>
<td>0 (0-0)</td>
</tr>
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</table>

Evidence statement(s):

The positive predictive values of having any childhood cancer ranged from 0.04% (for pain and musculoskeletal symptoms) to 2.19% (for hepatosplenomegaly) in all included patients aged 0-14 years, and from 0.061% (for lymphadenopathy) to 1.286% (for hepatosplenomegaly) for patients aged 0-4 years old, and from 0.049% (for bruising) to 0.154% (for ‘lump/mass/swelling’ [the PPV for hepatosplenomegaly could not be calculated as none of the controls experienced this symptom]) for
The positive predictive values of having leukaemia/lymphoma childhood cancer ranged from 0.01% (for fever and abdominal pain) to 0.53% (for bruising) for patients aged 0-14 years old; the positive predictive values of having young adulthood leukaemia ranged from 0.0117% (for bruising) to 0.0151% (for lymphadenopathy) for patients aged 15-24 years; and the positive predictive values of having young adulthood lymphoma ranged from 0.0279% (for ‘lump mass swelling below the neck excluding the abdomen’) to 0.5034% (for ‘lump mass swelling head and neck’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Tables 1-3).

The positive predictive values of having central nervous system childhood or young adulthood cancer tumours ranged from 0.02% (for seizure) to 0.11 (for abnormal movement) for patients aged 0-14 years old, and from 0.0029% (for pain) to 0.0238% (for seizure) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 7).

The positive predictive values of having childhood or young adulthood bone cancer tumour/soft tissue sarcoma ranged from 0% (for trauma) to 0.03% (for ‘lump mass swelling below neck excluding abdomen’) for patients aged 0-14 years old, and from 0.0027% (for chest pain) to 0.0415% (for ‘lump mass swelling’) for patients aged 15-24 years (1 study, N = 30855). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 8).

The positive predictive values of having childhood abdominal cancer tumours ranged from 0% (for childhood infection) to 0.03% (for bleeding and ‘lump mass swelling below neck excluding abdomen’) for patients aged 0-15 years old (1 study, N = 16585). The evidence quality is somewhat compromised by the case-control design of the study (see also Table 9).

Evidence tables

Dommett (2012; 2013a,b)

<table>
<thead>
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<th>PATIENT SELECTION</th>
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<tr>
<td>Patient sampling</td>
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<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td>For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Patient characteristics and Cases:</td>
</tr>
</tbody>
</table>
Cancer type: Leukemia: N = 368; brain: N = 270; lymphoma: N = 142; bone: N = 107; soft tissue sarcoma: N = 91; renal: N = 82; neuroblastoma: N = 75; other ICD codes: N = 132.

1064 teenagers and young adults (TYA): 15-24 years: Gender not reported.
Cancer type: Leukemia: N = 143; brain: N = 154; lymphoma: N = 270; bone: N = 96; soft tissue sarcoma: N = 100; other ICD codes: N = 301 (including testis: N = 60; skin: N = 49; ovary: N = 20 and thyroid: N = 17).

Controls:
15318 children; aged 0-4 years: N = 4802; aged 5-14 years: N = 10516; 8461 males/6857 females.
13206 TYA. Gender not reported

Inclusion criteria:
The sample comprised all children and TYU aged 0–24 years, inclusive, drawn from all general practices contributing research-standard data to the GPRD between 1 January 1988 and 31 December 2010. To be included, the practices had to have been contributing research-standard data for a minimum of 1 year before each child’s date of cancer diagnosis or the index date (see below) for matched controls.

Cases: Patients diagnosed with the following cancers: leukaemia, lymphoma, neuroblastoma, soft tissue sarcoma, hepatic, renal, bone and central nervous system tumours, using pre-defined medical codes used in the GPRD. The date of diagnosis for cases was defined as the date of pathological diagnosis, but if this was unavailable, the date of the first cancer code entered in the GPRD was used.

Controls: Up to 13 controls (children with no diagnosis of cancer at any time) were selected per case, using a computer-generated random sequence, matched on age (within 1 year), sex and practice, and had to be currently registered on the date of diagnosis of their matched case (the index date).

Exclusion criteria: None listed

Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
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**INDEX TEST**

**A. Risk of bias**

**Index test**
The GPRD uses just over 100 000 medical codes to encompass all primary care events, including both symptoms and diagnoses. From this list, libraries of codes were assembled representing individual alert symptoms derived from the NICE referral guidelines for suspected cancer in children. No more information reported.

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

For diagnostic case-control studies:
Investigators were kept 'blind' to other important confounding and prognostic factors? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation do not match the review question? Low concern
<table>
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<td>Cancer diagnosis in the UK’s General Practice Research Database.</td>
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<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
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<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
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<td><strong>B. Concerns regarding applicability</strong></td>
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<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
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<td><strong>FLOW AND TIMING</strong></td>
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<td>Flow and timing</td>
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<td>Was there an appropriate interval between index test and reference standard?</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
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<tr>
<td>Were all patients included in the analysis?</td>
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<td>Could the patient flow have introduced bias?</td>
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<td><strong>NOTES</strong></td>
<td>This study is published in three papers.</td>
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**References**

**Included studies**

**Excluded studies (with excl reason)**
Not in PICO
Narrative review
Erratum

Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


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Narrative review

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Narrative review

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Guideline

Narrative review

Narrative review

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Narrative review

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Narrative review

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Not in PICO

Narrative review

Not in PICO

Narrative review

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Narrative review

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Narrative review

syndrome-like features in bilateral wilms tumor are associated with inferior outcome. Pediatric 
Not in PICO

Narrative review
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journal of Indian Society of Medical & Paediatric Oncology, 33: 80-88.
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Narrative review?

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Simon, T. (555) [Neuroblastoma]. [Review] [7 refs] [German]. Urologe (Ausz.A), 44: 543-554.
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Narrative review

Narrative review

Not in PICO


Review question:
Which investigations of symptoms of suspected retinoblastoma, neuroblastoma and Wilm’s tumour in children should be done with clinical responsibility retained by primary care?

Results

Literature search

Retinoblastoma:

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Total References retrieved (after de-duplication): **28**

Wilm’s tumour: **Update Search**

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</table>

Total References retrieved (after de-duplication): **4**
Study results

No evidence was identified pertaining to the diagnostic accuracy of tests in children with suspected retinoblastoma, neuroblastoma and Wilm’s tumour where the clinical responsibility was retained by primary care.

References

Included studies

Excluded studies (with excl reason)


Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Narrative review

Narrative review

Narrative review

Narrative review

Narrative review

Not in PICO

Not in PICO

Not in PICO

Not in PICO

Narrative review

Not in PICO


Suspected Cancer: Appendix F (June 2015)

Not in PICO


Narrative review


Narrative review


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Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


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Narrative review


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Narrative review

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Narrative review

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Not in PICO

Not in PICO


Not in PICO


Not in PICO


Narrative review


Not in PICO


Narrative review


Outside of agreed date range (pre 1980)


Narrative review


Not in PICO


Narrative review


Not in PICO


Not in PICO


Not in PICO

Not in PICO


Outside of agreed date range (pre 1980)


Outside of agreed date range (pre 1980)


Narrative review


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO


Not in PICO
Not in PICO

Narrative review

Not in PICO
NON-SITE SPECIFIC SYMPTOMS

ABDOMINAL PAIN

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in some of the studies, with some studies also conducted in populations that are not clearly directly relevant to the current question and the quality of others suffering from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other issues to note concern missing data, the influence of which on the results is difficult to determine.

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of abdominal pain for cancer
<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/renal</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.2 (0.2-0.2)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Various*</td>
<td>30</td>
<td>84</td>
<td>1.524</td>
</tr>
<tr>
<td>Oesophagus/stomach</td>
<td>Meta-analysis</td>
<td>varied</td>
<td>varied</td>
<td>0.34 (0.16-0.71)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td>2.364</td>
</tr>
</tbody>
</table>

* Not sure which one to pick, so used average.

Table 2: Non-site specific symptoms of concern: Positive predictive values for abdominal pain

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Comme nt/relevant recs</th>
<th>Study</th>
<th>Symptom</th>
<th>Patient group</th>
<th>Positive predictive value% (95% CI)</th>
<th>Sex</th>
<th>Age inclusion, lower limit</th>
<th>Age inclusion, upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.11 (0.1-0.13)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>Men</td>
<td>0.2 (0.2-0.21)</td>
<td>men</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Collins (2013)</td>
<td>Abdominal pain</td>
<td>Women</td>
<td>0.1 (0.1-0.1)</td>
<td>women</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Hippisley-Cox (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.2 (0.2-0.2)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal pain (reported once)</td>
<td>All patients</td>
<td>1.1 (0.9-1.3)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal pain</td>
<td>Patients 40-69 years</td>
<td>0.65 (NR)</td>
<td>both</td>
<td>40</td>
<td>69</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal pain</td>
<td>Patients ≥ 70 years</td>
<td>2 (NR)</td>
<td>both</td>
<td>70</td>
<td>no upper limit</td>
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<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal pain (reported twice)</td>
<td>All patients</td>
<td>3 (1.8-5.2)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal pain and</td>
<td>All patients</td>
<td>1.4 (0.3-2.2)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Study</td>
<td>Cancer Type</td>
<td>Study Description</td>
<td>Abdominal tenderness</td>
<td>Patients</td>
<td>Sex</td>
<td>Outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>-------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Hamilton (2005)</td>
<td>Abdominal tenderness (reported once)</td>
<td>All patients</td>
<td>both</td>
<td>1.1 (0.8-1.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Collins (2013a)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>both</td>
<td>0.14 (0.12-0.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Collins (2013a)</td>
<td>Abdominal pain</td>
<td>Women</td>
<td>women</td>
<td>0.1 (0.09-0.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Collins (2013a)</td>
<td>Abdominal pain</td>
<td>Men</td>
<td>men</td>
<td>0.19 (0.16-0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Hippisley-Cox (2012b)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>both</td>
<td>0.3 (0.3-0.4)</td>
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<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Stapley (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>both</td>
<td>0.2 (0.19-0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Stapley (2012)</td>
<td>Abdominal pain</td>
<td>Patients ≥ 60 years</td>
<td>both</td>
<td>0.3 (0.3-0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Stapley (2012)</td>
<td>Abdominal pain (attended ≥ twice)</td>
<td>Patients ≥ 60 years</td>
<td>both</td>
<td>1 (0.8-1.2)</td>
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<td></td>
</tr>
</tbody>
</table>

**META-ANALYSES (1) Colorectal**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Type</th>
<th>Study Description</th>
<th>Abdominal pain</th>
<th>Patients</th>
<th>Sex</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Meta-analysis</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>2.04 (0.53-7.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Meta-analysis</td>
<td>Abdominal pain</td>
<td>All patients; w/o Panzuto (2003)</td>
<td>1.02 (0.38-2.69)</td>
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</tbody>
</table>

**The 4 studies below are those included in the meta-analysis reported in the cells above:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer Type</th>
<th>Study Description</th>
<th>Abdominal pain</th>
<th>Patients</th>
<th>Sex</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td></td>
<td>Bellentani (1990)</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>both</td>
<td>3.9 (2-7.3)</td>
</tr>
<tr>
<td>Source</td>
<td>Study Year</td>
<td>Pain Location</td>
<td>All Patients</td>
<td>Pain Duration</td>
<td>Gender</td>
<td>Median (Range)</td>
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<tr>
<td>-----------------------------</td>
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<td>----------------</td>
<td>--------------</td>
<td>---------------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>Colon</td>
<td>2012</td>
<td>Abdominal pain</td>
<td>0.5 (0.5-0.5)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Colon</td>
<td>2012a</td>
<td>Abdominal pain</td>
<td>0.7 (0.6-0.7)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Colon</td>
<td>2003</td>
<td>Abdominal pain</td>
<td>13.5 (9.4-18.8)</td>
<td>both</td>
<td>18</td>
<td>87</td>
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</tbody>
</table>

The following results are any extra analyses reported by the studies included in the above meta-analysis:

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Year</th>
<th>Pain Location</th>
<th>All Patients</th>
<th>Pain Duration</th>
<th>Gender</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>2012</td>
<td>Abdominal pain</td>
<td>0.6 (0.6-0.7)</td>
<td>men</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Colon</td>
<td>2012</td>
<td>Abdominal pain</td>
<td>0.4 (0.4-0.5)</td>
<td>women</td>
<td>30</td>
<td>84</td>
</tr>
</tbody>
</table>

**META-ANALYSES (2) Oesophageal**

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Year</th>
<th>Pain Location</th>
<th>All Patients</th>
<th>Pain Duration</th>
<th>Gender</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus/stomach</td>
<td>2012a</td>
<td>Abdominal pain</td>
<td>0.23 (0.14-0.36)</td>
<td>both</td>
<td>2 studies 30-84, 1 study 40- &gt;90</td>
<td></td>
</tr>
</tbody>
</table>

The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under stomach, avoid double counting it):

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Year</th>
<th>Pain Location</th>
<th>All Patients</th>
<th>Pain Duration</th>
<th>Gender</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal/stomach</td>
<td>2012a</td>
<td>Abdominal pain</td>
<td>0.2 (0.2-0.2)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Oesophageal/stomach</td>
<td>2011</td>
<td>Abdominal pain</td>
<td>0.3 (0.3-0.4)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>1981</td>
<td>Upper abdominal pain &gt; 2 weeks</td>
<td>0 (0-0.8)</td>
<td>both</td>
<td>40</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

The following results are any extra analyses reported by the studies included in the above meta-analysis:
### Analysis:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Oesophageal/stomach</th>
<th>Abdominal Pain</th>
<th>Women/Men</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal/stomach</td>
<td>Collins (2012a)</td>
<td>Abdominal pain</td>
<td>Women</td>
<td>0.1 (0.1-0.1)</td>
</tr>
<tr>
<td>Oesophageal/stomach</td>
<td>Collins (2012a)</td>
<td>Abdominal pain</td>
<td>Men</td>
<td>0.3 (0.3-0.3)</td>
</tr>
</tbody>
</table>

### Meta-Analyses (3) Stomach

<table>
<thead>
<tr>
<th>Oesophagus/stomach</th>
<th>Meta-analyses</th>
<th>Abdominal pain</th>
<th>All Patients</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus/stomach</td>
<td>2 combining gastro-oesophageal and 1 reporting on stomach cancer separately</td>
<td>Abdominal pain</td>
<td>All patients</td>
<td>0.34 (0.16-0.71)</td>
</tr>
</tbody>
</table>

The 3 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Collins (2012a) and Hippisley-Cox (2011) appear both here and under oesophageal, avoid double counting it):

<table>
<thead>
<tr>
<th>Oesophageal/stomach</th>
<th>Abdominal Pain</th>
<th>All Patients</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal/stomach</td>
<td>Collins (2012)</td>
<td>Abdominal pain</td>
<td>All patients</td>
</tr>
<tr>
<td>Oesophageal/stomach</td>
<td>Hippisley-Cox (2011)</td>
<td>Abdominal pain</td>
<td>All patients</td>
</tr>
<tr>
<td>Stomach</td>
<td>Møllmann (1981)</td>
<td>Upper abdominal pain &gt; 2 weeks</td>
<td>All patients</td>
</tr>
</tbody>
</table>

### Evidence Statement(s):

Abdominal pain (9 studies, N = 6248014) presenting in a primary care setting is associated with an overall positive predictive value of 2.364% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 1).

### Evidence Tables

Bellentani (1990)

### Patient Selection
### A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective consecutive patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | N = 254 (103 males/151 females); mean (SD) age of patients = Not reported; N = 140 were studied in primary care, N = 114 were referred to the gastroenterology services. It is unclear from the publication whether the patients who were referred to secondary care were a subset of “254 consecutive patients who presented to their GP during the study period for chronic abdominal pain” or whether they are recruited directly from secondary care (see Inclusion criteria). |

**Inclusion criteria:** All consecutive patients consulting 14 GPs of the local health district, taking care of 14000 citizens, or referred to the outpatient clinic of the Gastroenterology Unit, either complaining of recurrent abdominal pain or having intestinal problems (as judges by the GP), between January 1987 and March 1988.

**Exclusion criteria:** Patients with acute abdomen, acute gastroenteritis or a clear cut diagnosis of upper gastrointestinal tract disease (gastritis, oesophagitis, peptic ulcer, or dyspepsia).

**Clinical setting:** Primary/secondary care, Italy.

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

#### INDEX TEST

##### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>Recurrent abdominal pain or intestinal problems (as judges by the GP; not further specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

##### B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Unclear concern |

#### REFERENCE STANDARD

##### A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Double-contrast barium enema or colonoscopy no more than 2 months after the enrolment in the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear (but all patients had a positive index test)</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for in the results but the number of true negatives and false negatives could not be ascertained from the reported results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

Collins (2012)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### Patient characteristics and setting

A total of 2135540 patients were identified from 364 practices. **Symptoms:**
- Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670).

**Incident cases of colorectal cancer during the 2-year follow up period:**
N = 3712 (2036 men, 1676 women).

**Inclusion criteria:**
Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

**Exclusion criteria:**
Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

**Clinical setting:** Primary care, UK

### Are there concerns that the included patients and setting do not match the review question?

Low concern

### INDEX TEST

#### A. Risk of bias

| Index test | ‘Red-flag’ symptoms: Rectal bleeding, loss of appetite, weight loss, abdominal pain, change in bowel habit (men only), and anaemia. |

---

Suspected Cancer: Appendix F (June 2015) Page 1637 of 1735
| **Were the index test results interpreted without knowledge of the results of the reference standard?** | Yes |
| **Could the conduct or interpretation of the index test have introduced bias?** | Low risk |

**B. Concerns regarding applicability**

| **Are there concerns that the index test, its conduct, or interpretation differ from the review question?** | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients seem to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

The is very large, if not complete, overlap of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)

Collins (2012a)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; |
Incident cases of gastro-oesophageal cancer during the 2-year follow up period:
N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer).

Inclusion criteria:
Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

Exclusion criteria: Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates.

Clinical setting: Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?**

| Low concern |

**INDEX TEST**

**A. Risk of bias**

**Index test**
‘Red-flag’ symptoms: Haematemesis, dysphagia, loss of appetite, weight loss, anaemia, and abdominal pain.

| Yes |

**Could the conduct or interpretation of the index test have introduced bias?**

| Low risk |

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**

| Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

**Reference standard(s)**
2-year follow up

| Yes |

**Is the reference standard likely to correctly classify the target condition?**

| Yes |

**Were the reference standard results interpreted without knowledge of the results of the index tests?**

| Unclear |

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

| Low risk |

**B. Concerns regarding applicability**

**Are there concerns that the target condition as defined by the reference standard does not match the question?**

| Low concern |

**FLOW AND TIMING**

**A. risk of bias**

**Flow and timing**
All patients seem to be accounted for

| Yes |

**Was there an appropriate interval between index test and reference standard?**

| Yes |

**Did all patients receive the same reference standard?**

| Yes |

**Were all patients included in the analysis?**

| Yes |
Could the patient flow have introduced bias? | Low risk
---|---
**NOTES** | The study did not distinguish between gastric and oesophageal cancer

**Collins (2013)**

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling | Retrospective patient series using the THIN database.
---|---
Was a consecutive or random sample of patients enrolled? | Yes
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting | A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices.
---|---
Symptoms: | Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women).
Incident cases of renal tract cancer during the 2-year follow up period: | N = 2283 (1685 men, 598 women).
Inclusion criteria: | Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period.
Exclusion criteria: | Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old.
Clinical setting: | Primary care, UK

Are there concerns that the included patients and setting do not match the review question? | Low concern

**INDEX TEST**

**A. Risk of bias**

Index test | ‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.
---|---
Were the index test results interpreted without knowledge of the results of the reference standard? | Yes
Could the conduct or interpretation of the index test have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern
### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients seem to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
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<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

**Collins (2013a)**

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
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<td>Was a case-control design avoided?</td>
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<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 2150322 patients were identified from 364 practices. Symptoms: Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326). Incident cases of pancreatic cancer during the 2-year follow up period: N = 287 (331 men, 287 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the |

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Suspected Cancer: Appendix F (June 2015)  Page 1641 of 1735
study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

Exclusion criteria: Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates.

Clinical setting: Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDEX TEST</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>‘Red-flag’ symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>2-year follow up</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>All patients seem to be accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

Hamilton (2005)

PATIENT SELECTION

A. Risk of bias

Patient sampling | Population-based matched case-control study involving all 21 general
<table>
<thead>
<tr>
<th>practice in Exeter, Devon, UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to</td>
</tr>
<tr>
<td>balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all</td>
</tr>
<tr>
<td>major confounding and prognostic factors?</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases:</th>
<th>Controls:</th>
<th>Inclusion criteria:</th>
<th>Exclusion criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 349 (177 males/172 females), age at diagnosis: &lt; 60 years: N = 45, 60-69 years: N = 97, 70-79 years: N = 113, 80+ years: N = 94. 210/349 had tumours at or distal to the splenic flexure, and 126/349 had tumours proximal to the splenic flexure, the remaining 13/349 has tumours in multiple or unknown sites. Duke’s staging was known for 305/349: 170/305 were Duke’s A or B, and 135/305 were Duke’s C or D.</td>
<td>N = 1744 (885 males/859 females), age at diagnosis: &lt; 60 years: N = 225, 60-69 years: N = 487, 70-79 years: N = 555, 80+ years: N = 477.</td>
<td>All patients aged ≥ 40 years with a primary colorectal cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case.</td>
<td>Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous colorectal cancer; or residence outside Exeter at the time of diagnosis. Clinical setting: Primary care, UK.</td>
</tr>
</tbody>
</table>

**Are there concerns that the included patients and setting do not match the review question?** | **Low concern** |

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.</th>
</tr>
</thead>
</table>

**Were the index test results interpreted without knowledge of the results of the reference standard?** | **Yes** |
<table>
<thead>
<tr>
<th>For diagnostic case-control studies:</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td>Low concern</td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

### REFERENCE STANDARD

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Colorectal cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

- Hippisley-Cox (2011)
- **PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current dysphagia (N = 8165), current haematemesis (N = 7119), current |
Suspected Cancer: Appendix F (June 2015)

Abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the last year (N = 218862.

Incident cases of gastro-oesophageal cancer during the 2-year follow up period:
N = 1343 (776 oesophageal and 567 gastric).

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care, UK

Are there concerns that the included patients and setting do not match the review question? | Low concern
-----|-----

INDEX TEST

A. Risk of bias

Index test

‘Red-flag’ symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes

Could the conduct or interpretation of the index test have introduced bias? | Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

REFERENCE STANDARD

A. Risk of bias

Reference standard(s) | 2-year follow up

Is the reference standard likely to correctly classify the target condition? | Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question?  Low concern

FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

NOTES
Results not presented separately for gastric and oesophageal cancer

Hippisley-Cox (2012)

PATIENT SELECTION

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
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<tbody>
<tr>
<td>Patient sampling</td>
<td>Prospective patient series using patients in the QResearch database (version 30).</td>
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<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
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<td>Could the selection of patients have introduced bias?</td>
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</tbody>
</table>

B. Concerns regarding applicability

| Patient characteristics and setting | A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169). Incident cases of renal tract cancer during the 2-year follow up period: N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2. Inclusion criteria: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from |
patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

| Flow and timing | A total of 1342329 patients were initially identified of whom 101607 patients |---|---|
were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

Was there an appropriate interval between index test and reference standard? Yes
Did all patients receive the same reference standard? Yes
Were all patients included in the analysis? No
Could the patient flow have introduced bias? High risk

NOTES

Hippisley-Cox (2012a)

PATIENT SELECTION

A. risk of bias
Patient sampling

Prospective patient series using patients in the QResearch database (version 30).

Was a consecutive or random sample of patients enrolled? Yes
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk

B. Concerns regarding applicability

Patient characteristics and setting

A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).

Symptoms:
Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821).

Incident cases of colorectal cancer during the 2-year follow up period:
N = 2603 (1562 colon and 1041 rectum).

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.
<table>
<thead>
<tr>
<th>Clinical setting: Primary care, UK</th>
</tr>
</thead>
</table>

**Are there concerns that the included patients and setting do not match the review question?**

| Low concern |

**INDEX TEST**

**A. Risk of bias**

**Index test**

‘Red-flag’ symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months).

Was the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

**REFERENCE STANDARD**

**A. Risk of bias**

Reference standard(s) 2-year follow up

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

**FLOW AND TIMING**

**A. Risk of bias**

Flow and timing A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? No

Could the patient flow have introduced bias? Low risk

**NOTES**

Please note there is some overlap between this patient sample and that of Parker (2007)
### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td><strong>Low risk</strong></td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

**Patient characteristics and setting**

A total of 12,437,40 patients were identified from 189 practices (62,435 males, 61,938 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).

Current symptoms and symptoms in the preceding year:
- Current dysphagia (N = 8507), current abdominal pain (N = 129,924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14,686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12,233), tiredness in the last year (N = 12,688), itching in the last year (N = 1,454), haemoglobin recoded in the last year (N = 214,497), haemoglobin < 11 g/dl in the last year (N = 16,172).

Incident cases of pancreatic cancer during the 2-year follow up period: N = 781.

**Inclusion criteria:**
- All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included.
- Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry.
- For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

**Exclusion criteria:**
- Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

**Clinical setting:** Primary care

---

**INDEX TEST**

#### A. Risk of bias

| Index test | ‘Red-flag’ symptoms were defined as symptoms that might alarm the patient |

---

**Are there concerns that the included patients and setting do not match the review question?**

**Low concern**
and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or its interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s) Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).</td>
<td></td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing A total of 1342329 patients were initially identified of whom 98589 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</td>
<td></td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**NOTES**

Møllmann (1981)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling Prospective patient series from an open-access gastroscopy clinic in</td>
<td></td>
</tr>
<tr>
<td><strong>Denmark.</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years N = 47; 90- years: N = 8.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong> All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain &gt; 2 weeks, nausea and/or vomiting &gt; 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb &lt; 80%).</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Patients who had been examined for any of the above symptoms within the last 6 months.</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical setting:</strong> GPs in Denmark</td>
<td></td>
</tr>
</tbody>
</table>

| **Are there concerns that the included patients and setting do not match the review question?** | Unclear concern |

**INDEX TEST**

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
<td>Upper abdominal pain &gt; 2 weeks, nausea and/or vomiting &gt; 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb &lt; 80%).</td>
</tr>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</strong></td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th><strong>A. risk of bias</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference standard(s)</strong></td>
<td>2-stage process: Gastroscopy with photography, using a gastroscope, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.</td>
</tr>
<tr>
<td><strong>Is the reference standard likely to correctly classify the target condition?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Were the reference standard results interpreted without knowledge of the results of the index tests?</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Are there concerns that the target condition as defined by the reference standard does not match the question?</strong></td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**FLOW AND TIMING**
### A. risk of bias

#### Flow and timing

177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes probably</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported. This research was published in 2 papers.

---

### Panzuto (2003)

#### PATIENT SELECTION

### A. risk of bias

#### Patient sampling

Prospective 8-week study of patients presenting to 159 primary care physicians (approximately 63600 patient visits during the study period in total) in Italy.

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

#### Patient characteristics and setting

N = 280; 120 males, 160 females; median age (range) = 61 (18-87) years.

**Inclusion criteria:** Consecutive patients who consulted their GP “with symptoms considered suspicious for the presence of a colon disease to rule out the presence of colorectal cancer” and who were investigated with a colonoscopy or double-contrast barium enema [The decision of how (colonoscopy or double-contrast barium enema) and when to investigate the colon was made only by the physicians on the basis of the clinical evaluation during the visit].

**Exclusion criteria:** Patients with previous diagnoses of colorectal disorders or a recent large bowel examination.

**Clinical setting:** Primary care, Italy.

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

#### INDEX TEST

### A. Risk of bias

#### Index test

Abdominal pain, bloating, constipation, rectal bleeding, diarrhoea, iron-deficiency anaemia (haemoglobin levels < 14 g/dl for males and < 12 g/dl for females, in the presence of ferritin < 30 µg/l and a median corpuscular value < 80 fl), change in bowel habits (onset of diarrhoea or constipation or altered stool in the previous 3 months) and weight loss (decrease of ≥ 3 kg in the 3 months prior to the visit).

| Were the index test results interpreted without knowledge | Yes |
of the results of the reference standard?

| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**FLOW AND TIMING**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>56/332 patients were excluded due to lack of mandatory fields (age, sex, clinical history, presenting symptoms and procedure results) in the database (N = 35) or violation of exclusion criteria (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

Stapley (2012)

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td></td>
<td>For diagnostic case-control studies:</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

#### Patient characteristics and setting

| Cases: | N = 3635, 1743 males / 1892 females; median number of consultations = 18 (IQR = 11-27); aged 40-49 years: N = 107; 50-59 years: N = 529; 60-69 years: N = 829; 70-79 years: N = 1212; ≥ 80 years: N = 958; UK. |
| Controls: | N = 16459, gender not reported; median number of consultations = 9 (IQR = 4-15); aged 40-49 years: N = 422; 50-59 years: N = 2239; 60-69 years: N = 3755; 70-79 years: N = 5702; ≥ 80 years: N = 4341; UK. |

**Inclusion criteria:**

Cases: Patients with a record of one of 25 GPRD pancreatic cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a pancreatic cancer code was assigned the data of diagnosis/index date.

Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.

**Exclusion criteria:** Pancreatic cancer (controls), no consultations in the year before diagnosis.

**Clinical setting:** Primary care

#### Are there concerns that the included patients and setting do not match the review question?

Low concern

### INDEX TEST

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>All symptoms, physical signs or abnormal investigations compiled from the pancreatic cancer literature were studied, and supplemented by discussion with two pancreatic cancer charities. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ≥5% of cases or controls. Repeat attendances with the same symptom were also retained if the subsequent consultation also occurred in ≥5% of cases or controls. New-onset diabetes was defined as a code for diabetes, or a random blood glucose above the local laboratory’s normal range, without similar codes more than 1 year before the index date. For laboratory tests, patients without a test were considered to be the same status as those with a normal result, making our binary variable abnormal result/ no abnormal result. Abnormal liver function was defined as any liver enzyme above the normal range, and raised inflammatory markers as either abnormal erythrocyte sedimentation rate or C-reactive protein, as there were too few plasma viscosity results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

#### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
<td>Pancreatic cancer code in the UK’s General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

#### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>A total of 21624 patients were identified, 17977 controls and 3647 cases. Of the controls the following exclusions were applied: pancreatic cancer (N = 64), case excluded (N = 40), and no data in year pre-index date (N = 1414). Of the cases the following exclusions were applied: No controls (N = 2), and cancer not of pancreatic origin (N = 10).</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

**References**

**Included studies**


APPETITE LOSS

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in one of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by this study are however likely to have gone some way in addressing this issue.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/renal</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.18 (0.07-0.4)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton* (2005)</td>
<td>40</td>
<td>no upper limit</td>
<td>1.285</td>
</tr>
<tr>
<td>Oesophagus/stomach</td>
<td>Hippisley-Cox (2011)</td>
<td>30</td>
<td>84</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>Cancer site</td>
<td>Comment/relevant recs</td>
<td>Study</td>
<td>Symptom</td>
<td>Patient group</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------</td>
<td>-------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td>Collins (2013)</td>
<td>Appetite loss</td>
<td>Women</td>
<td>0.1 (0.04-0.3)</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td>Hippisley-Cox (2012)</td>
<td>Appetite loss</td>
<td>All patients</td>
<td>0.18 (0.07-0.4)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hippisley-Cox (2012)</td>
<td>Loss of appetite</td>
<td>All patients</td>
<td>0.9 (0.6-1.2)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Collins (2012)</td>
<td>Loss of appetite</td>
<td>All patients</td>
<td>0.8 (0.6-1.1)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Collins (2012)</td>
<td>Loss of appetite</td>
<td>Men 30-84 years</td>
<td>1 (0.6-1.5)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Collins (2012)</td>
<td>Loss of appetite</td>
<td>Women 30-84 years</td>
<td>0.6 (0.4-1)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>Appetite loss</td>
<td>All included patients</td>
<td>0.87 (0.6-1.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>Appetite loss (reported twice)</td>
<td>All included patients</td>
<td>1.7 (NR)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>Appetite loss</td>
<td>Patients 40-69 years</td>
<td>1.1 (NR)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>Appetite loss</td>
<td>All smokers</td>
<td>1.8 (NR)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>Appetite loss</td>
<td>All smokers</td>
<td>2.7 (NR)</td>
</tr>
</tbody>
</table>

* Not sure which one to pick, so used average.

Table 2: Non-site specific symptoms of concern: Positive predictive values for appetite loss
Evidence statement(s):

Appetite loss (5 studies, N = 4961516) presenting in a primary care setting is associated with an overall positive predictive value of 4.65% for cancer. The studies were associated with 0-1 bias/applicability concern (see also Table 1).

Evidence tables

Collins (2012)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
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<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
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</table>

B. Concerns regarding applicability
A total of 2135540 patients were identified from 364 practices.

**Symptoms:**
Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670).

**Incident cases of colorectal cancer during the 2-year follow up period:**
N = 3712 (2036 men, 1676 women).

**Inclusion criteria:**
Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

**Exclusion criteria:**
Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

**Clinical setting:** Primary care, UK

| **Patient characteristics and setting** | **A total of 2135540 patients were identified from 364 practices.** |
| **Symptoms:** | **Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670).** |
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**Clinical setting:** Primary care, UK
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</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

The is **very large, if not complete, overlap** of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009).

**Collins (2012a)**

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling: Retrospective patient series using the THIN database.

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of patients have introduced bias? Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting: A total of 2135540 patients were identified from 364 practices.

**Symptoms:**
- Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 12938 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women).
- **Incident cases of gastro-oesophageal cancer during the 2-year follow up period:**
  - N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer).
- **Inclusion criteria:**
  - Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.
- **Exclusion criteria:** Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates.
- **Clinical setting:** Primary care, UK

Are there concerns that the included patients and setting do not match the review question? Low concern

**INDEX TEST**

**A. Risk of bias**


Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk
### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients seem to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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</tr>
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<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

- The study did not distinguish between gastric and oesophageal cancer

Collins (2013)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period: N = 2283 (1685 men, 598 women). |

---

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**Inclusion criteria:**
Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period.

**Exclusion criteria:** Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old.

**Clinical setting:** Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**
‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |

| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**
Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.

| Is the reference standard likely to correctly classify the target condition? | Yes |

| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |

| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. Risk of bias**

**Flow and timing**
All patients seem to be accounted for.

| Was there an appropriate interval between index test and reference standard? | Yes |

| Did all patients receive the same reference standard? | Yes |

| Were all patients included in the analysis? | Yes |
Could the patient flow have introduced bias?  |  Low risk
--- | ---

**NOTES**
It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

**Collins (2013a)**

**PATIENT SELECTION**

**A. risk of bias**

**Patient sampling**
Retrospective patient series using the THIN database.

Was a consecutive or random sample of patients enrolled?  |  Yes
--- | ---

Was a case-control design avoided?  |  Yes
--- | ---

Did the study avoid inappropriate exclusions?  |  Yes
--- | ---

**Could the selection of patients have introduced bias?**  |  Low risk
--- | ---

**B. Concerns regarding applicability**

**Patient characteristics and setting**
A total of 2150322 patients were identified from 364 practices.

**Symptoms:**
Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326).

**Incident cases of pancreatic cancer during the 2-year follow up period:**
N = 287 (331 men, 287 women).

**Inclusion criteria:**
Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

**Exclusion criteria:**
Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates.

**Clinical setting:**
Primary care, UK

**Are there concerns that the included patients and setting do not match the review question?**  |  Low concern
--- | ---

**INDEX TEST**

**A. Risk of bias**

**Index test**
‘Red-flag’ symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).

**Were the index test results interpreted without knowledge of the results of the reference standard?**  |  Yes
--- | ---

**Could the conduct or interpretation of the index test have introduced bias?**  |  Low risk
--- | ---

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**  |  Low concern
--- | ---

**REFERENCE STANDARD**

**A. risk of bias**

**Reference standard(s)**
2-year follow up
### Patient Selection

#### A. Risk of Bias

**Patient Sampling**  
Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attemps were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

#### B. Concerns Regarding Applicability

- **Patient characteristics and setting**
  - **Cases:**  
    N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34.  
  - **Controls:**  
  - **Inclusion criteria:**  
    Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register.
Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case.
Exclusion criteria:
Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis.
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**
Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>For diagnostic case-control studies:</em> Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

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<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**
Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
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</tr>
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</table>

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
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</tbody>
</table>
### Patient Selection

#### A. Risk of Bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
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</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns Regarding Applicability

- **Patient characteristics and setting**: A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6).

  - **Symptoms**: Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638), haemoglobin < 11 g/dl in the last year (N = 218862).

  - **Incident cases of gastro-oesophageal cancer during the 2-year follow-up period**: N = 1343 (776 oesophageal and 567 gastric).

  - **Inclusion criteria**: All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. *The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.*

  - **Exclusion criteria**: Patients without a postcode-related Townsend score, patients with a history of gastro-oesophageal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

  - **Clinical setting**: Primary care, UK

- **Are there concerns that the included patients and setting do not match the review question?** Low concern

### Index Test

#### A. Risk of Bias

<table>
<thead>
<tr>
<th>Index test</th>
<th>‘Red-flag’ symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge</td>
<td>Yes</td>
</tr>
</tbody>
</table>
of the results of the reference standard? | Low risk
---|---
Could the conduct or interpretation of the index test have introduced bias? |  
B. Concerns regarding applicability
Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**REFERENCE STANDARD**

| A. risk of bias |  
---|---
Reference standard(s) | 2-year follow up
Is the reference standard likely to correctly classify the target condition? | Yes
Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

| B. Concerns regarding applicability |  
---|---
Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**FLOW AND TIMING**

| A. risk of bias |  
---|---
Flow and timing | A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.
Was there an appropriate interval between index test and reference standard? | Yes
Did all patients receive the same reference standard? | Yes
Were all patients included in the analysis? | No
Could the patient flow have introduced bias? | Unclear risk

**NOTES** | Results not presented separately for gastric and oesophageal cancer

**Hippisley-Cox (2012)**

**PATIENT SELECTION**

| A. risk of bias |  
---|---
Patient sampling | Prospective patient series using patients in the QResearch database (version 30).
Was a consecutive or random sample of patients enrolled? | Yes
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Low risk

| B. Concerns regarding applicability |  
---|---
A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).

Current symptoms and symptoms in the preceding year:
Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recorded in the last year (N = 216201), haemoglobin < 11 g/dl in the last year (N = 16169).

Incident cases of renal tract cancer during the 2-year follow up period:
N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Are there concerns that the included patients and setting do not match the review question? Low concern

INDEX TEST

A. Risk of bias

Index test
‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

REFERENCE STANDARD

A. Risk of bias

Reference Renal tract cancer, which was defined as incident diagnosis of cancer of the...
standard(s)  bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).

Is the reference standard likely to correctly classify the target condition?  Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?  Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias?  Low risk

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?  Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing  A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

Was there an appropriate interval between index test and reference standard?  Yes

Did all patients receive the same reference standard?  Yes

Were all patients included in the analysis?  No

Could the patient flow have introduced bias?  High risk

NOTES

Hippisley-Cox (2012a)

PATIENT SELECTION

A. risk of bias

Patient sampling  Prospective patient series using patients in the QResearch database (version 30).

Was a consecutive or random sample of patients enrolled?  Yes

Was a case-control design avoided?  Yes

Did the study avoid inappropriate exclusions?  Yes

Could the selection of patients have introduced bias?  Low risk

B. Concerns regarding applicability

Patient characteristics and setting  A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).

Symptoms:  Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent
change in bowel habit (N = 1821).

Incident cases of colorectal cancer during the 2-year follow up period:
N = 2603 (1562 colon and 1041 rectum).

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care, UK

| Are there concerns that the included patients and setting do not match the review question? | Low concern |
| A. Risk of bias | |
| **Index test** | ‘Red-flag’ symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months). |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| **B. Concerns regarding applicability** | |
| **REFERENCE STANDARD** | |
| A. risk of bias | 2-year follow up |
| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| **Could the reference standard, its conduct, or its interpretation have introduced bias?** | Low risk |
| **B. Concerns regarding applicability** | |
| **Are there concerns that the target condition as defined by the reference standard does not match the question?** | Low concern |
**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

**NOTES**

Please note there is some overlap between this patient sample and that of Parker (2007)

---

**Hippisley-Cox (2012b)**

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Current symptoms and symptoms in the preceding year: Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recorded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172). Incident cases of pancreatic cancer during the 2-year follow up period: N = 781. |
| Inclusion criteria: | All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from |
patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

| Flow and timing | A total of 1342329 patients were initially identified of whom 98589 patients |
were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | No |
| Could the patient flow have introduced bias? | High risk |

### Notes

**References**

**Included studies**


WEIGHT LOSS AND APPETITE LOSS

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not based on a consecutive or random series of patients in one of the studies, while the other study was conducted in a population that is not necessarily directly relevant to the current question. Studies employing non-consecutive/random sampling are at high risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of appetite loss with weight loss for cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>40</td>
<td>no upper limit</td>
<td>2.3 (1.2-4.4)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Möllmann (1981)</td>
<td>40</td>
<td>&gt;90</td>
<td>0 (0-8.9) 0/50</td>
</tr>
<tr>
<td>Stomach</td>
<td>Möllmann (1981)</td>
<td>40</td>
<td>&gt;90</td>
<td>2 (0.1-12) 1/50</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
</tbody>
</table>

Table 2: Non-site specific symptoms of concern: Positive predictive values for weight loss + appetite loss

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Comment/relevant recs</th>
<th>Study</th>
<th>Symptom</th>
<th>Patient group</th>
<th>Positive predictive value% (95% CI)</th>
<th>Sex</th>
<th>Age inclusion, lower limit</th>
<th>Age inclusion, upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Rec: Offered FBC and xray</td>
<td>Hamilton (2005)</td>
<td>Weight loss + appetite loss</td>
<td>All included patients</td>
<td>2.3 (1.2-4.4)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
</tbody>
</table>
Evidence statement(s):

Appetite loss with weight loss (2 studies, N = 2962) presenting in a primary care setting is associated with an overall positive predictive value of 4.3% for cancer. The studies were associated with 1-3 bias/applicability concerns (see also Table 1).

Evidence tables

Hamilton (2005)

<table>
<thead>
<tr>
<th>Lung</th>
<th>Rec: Offered FBC and xray</th>
<th>Hamilton (2005)</th>
<th>Weight loss + appetite loss</th>
<th>All smokers</th>
<th>5 (NR)</th>
<th>both</th>
<th>40</th>
<th>no upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>Rec: Møllmann (1981)</td>
<td>Weight loss and/or anorexia</td>
<td>All patients</td>
<td>0 (0-8.9)</td>
<td>both</td>
<td>40</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>Rec: UGI endoscopy</td>
<td>Møllmann (1981)</td>
<td>Weight loss and/or anorexia</td>
<td>All patients</td>
<td>2 (0.1-12)</td>
<td>both</td>
<td>40</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

Evidence statement(s):

Appetite loss with weight loss (2 studies, N = 2962) presenting in a primary care setting is associated with an overall positive predictive value of 4.3% for cancer. The studies were associated with 1-3 bias/applicability concerns (see also Table 1).

Evidence tables

Hamilton (2005)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 247 (170 males/77 females), age at diagnosis: &lt; 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34.</td>
<td></td>
</tr>
<tr>
<td>Controls:</td>
<td></td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td></td>
</tr>
<tr>
<td>Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register.</td>
<td></td>
</tr>
</tbody>
</table>
Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case. Exclusion criteria:
Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis.
Clinical setting: Primary care, UK.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

#### A. Risk of bias

**Index test**

Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>For diagnostic case-control studies: Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### REFERENCE STANDARD

#### A. Risk of bias

**Reference standard(s)**

Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### FLOW AND TIMING

#### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>
### Notes

Møllmann (1981)

### Patient Selection

#### A. Risk of Bias

**Patient Sampling**

Prospective patient series from an open-access gastroscopy clinic in Denmark.

<table>
<thead>
<tr>
<th>Was a consecutive or random sample of patients enrolled?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns Regarding Applicability

| Patient characteristics and setting | N = 1480; gender not reported; 40-44 years: N = 144; 45-49 years: N = 186; 50-69 years: N = 882; 70-74 years: N = 130; 75-79 years: N = 83; 80-89 years: N = 47; 90-99 years: N = 8. |

**Inclusion Criteria:** All patients who, for a 2-year period, presented to their GP with (any of) the following symptoms were referred to the open access gastroscopy clinic: Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).

**Exclusion Criteria:** Patients who had been examined for any of the above symptoms within the last 6 months.

**Clinical Setting:** GPs in Denmark

Are there concerns that the included patients and setting do not match the review question? Unclear concern

### Index Test

#### A. Risk of Bias

**Index Test**

Upper abdominal pain > 2 weeks, nausea and/or vomiting > 2 weeks, weight loss and/or anorexia, gastrointestinal bleeding, and anaemia (i.e., Hb < 80%).

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns Regarding Applicability

Are there concerns that the index test, its conduct, or its interpretation differ from the review question? Low concern

### Reference Standard

#### A. Risk of Bias

**Reference Standard(s)**

2-stage process: Gastroscopy with photography, using a gastrocamera, performed with only local anaesthesia of the pharynx. If this investigation disclosed abnormal conditions, the next stage was gastroscopy, possibly with biopsy, using diazepam sedation.

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation differ from the review question?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>
B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

FLOW AND TIMING

A. risk of bias

Flow and timing 177/1480 patients declined endoscopy, 2/1480 did not show up for endoscopy, and it was unsuccessful in a further 24 patients, leaving 1277 patients. However, the paper reports that only 1273 had primary endoscopy, and then reports the results for between 1181 and 1297 patients.

Was there an appropriate interval between index test and reference standard? Yes probably

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? No

Could the patient flow have introduced bias? High risk

NOTES There were a total of 18 gastric cancers confirmed in the study. No oesophageal cancers were reported. This research was published in 2 papers.

References

Included studies

The data split by smoking status is available from:


DEEP VEIN THROMBOSIS

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised in the figure below. The main validity issue to note is that the study was conducted in the Netherlands and the findings are only applicable to the extent that the study population and setting are comparable to a UK GP population as defined for the current purposes.

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of deep vein thrombosis for cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Oudega (2006)</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td>0.7 (0.2-2.2)</td>
<td></td>
</tr>
<tr>
<td>Urogenital</td>
<td>Oudega (2006)</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td>1.16 (0.4-2.9)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Oudega (2006)</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td>0.93 (0.3-2.53)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Oudega (2006)</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td>0.7 (0.2-2.2)</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td>3.49</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Non-site specific symptoms of concern: Positive predictive values for deep vein thrombosis

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Comme nt/relev ant recs</th>
<th>Study</th>
<th>Symptom</th>
<th>Patient group</th>
<th>Positive predictive value% (95% CI)</th>
<th>Sex</th>
<th>Age inclusion, lower limit</th>
<th>Age inclusion, upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td></td>
<td>Oudega (2006)</td>
<td>Deep vein thrombosis</td>
<td>All included patients</td>
<td>0.7 (0.2-2.2)</td>
<td>both</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td></td>
</tr>
<tr>
<td>Urogenital</td>
<td></td>
<td>Oudega (2006)</td>
<td>Deep</td>
<td>All</td>
<td>1.16 (0.4-2.9)</td>
<td>both</td>
<td>No age incl/excl given, sample mean (SD) age = 60.7 (18.2) years</td>
<td></td>
</tr>
</tbody>
</table>
Evidence statement(s):

Deep vein thrombosis (1 study, N = 430) presenting in a primary care setting is associated with an overall positive predictive value of 3.49% for cancer. The study was associated with 1 applicability concern (see also Table 1).

Evidence tables

Oudega (2006)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. risk of bias</td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: Consecutive patients who consulted their GP between January 1996 and July 2002 and who, after investigation (not referral) was confirmed to have deep vein thrombosis.</td>
</tr>
<tr>
<td>Exclusion criteria: Patients with a known malignancy or a malignancy detected within 2 weeks of deep vein thrombosis diagnosis.</td>
</tr>
<tr>
<td>Clinical setting: Primary care, The Netherlands.</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
</tr>
</tbody>
</table>
### INDEX TEST

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong></td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or its interpretation differ from the review question?</td>
</tr>
</tbody>
</table>

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
</tr>
</tbody>
</table>

### FLOW AND TIMING

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
</tr>
</tbody>
</table>

### NOTES

In total N = 19 had cancer: 3 colorectal, 5 urogenital (not further subgrouped), 4 breast, 3 lung and 4 other. The urogenital data is added to the renal cancer evidence review.

### References

**Included studies**
DYSPEPSIA

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and the vast majority of the studies were conducted in populations that are not clearly directly relevant to the current question. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. Studies conducted in other settings than UK-based primary care are only applicable to the extent that the study populations and settings are comparable to a UK GP population as defined for the current purposes. Other bias and applicability threats to the results concern missing data and a potentially suboptimal reference standard.

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of dyspepsia for cancer

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hallissey (1990)</td>
<td>40</td>
<td>no upper limit</td>
<td>0.04 (0.002-0.25)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Hallissey (1990)</td>
<td>40</td>
<td>no upper limit</td>
<td>0.23 (0.09-0.53)</td>
</tr>
<tr>
<td>Uterine</td>
<td>Hallissey (1990)</td>
<td>40</td>
<td>no upper limit</td>
<td>0.04 (0.002-0.25)</td>
</tr>
<tr>
<td>Cancer site</td>
<td>Comment/relevant recs</td>
<td>Study</td>
<td>Symptom</td>
<td>Patient group</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------</td>
<td>----------------------------</td>
<td>---------</td>
<td>---------------</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Pancreatic</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Uterine</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Leukaemia</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Gall bladder</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Bronchial</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia</td>
<td>All patients</td>
</tr>
</tbody>
</table>

**META-ANALYSES (1) Oesophageal**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Comment/relevant recs</th>
<th>Study</th>
<th>Symptom</th>
<th>Patient group</th>
<th>Positive predictive value% (95% CI)</th>
<th>Sex</th>
<th>Age inclusion, lower limit</th>
<th>Age inclusion, upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus/stomach</td>
<td>2 combining gastro-</td>
<td>Meta-analysis</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.25 (0.13-0.5)</td>
<td>both</td>
<td>2 studies &gt; 15, 2 studies &gt; 18, 1 study &gt; 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18- &gt;65, 1 study NR but</td>
<td></td>
</tr>
</tbody>
</table>
The 11 studies below are those included in the meta-analysis reported in the cell above. Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under stomach, avoid double counting it:

<table>
<thead>
<tr>
<th>Oesophageal and gastric reporting on oesophageal cancer separately</th>
<th>Dyspepsia</th>
<th>All patients</th>
<th>Mean (SD) age = 41-42 (15-16) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal</td>
<td>Brignoli (1997)</td>
<td>Dyspepsia</td>
<td>0.58 (0.33-0.98)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Duggan (2008)</td>
<td>Dyspepsia</td>
<td>0.61 (0.03-3.8)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Edenhholm (1985)</td>
<td>Persistent epigastric pain/ ulcer-like dyspepsia</td>
<td>0.58 (0.33-0.98)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Hallissey (1990)</td>
<td>Dyspepsia</td>
<td>0.54 (0.25-1.1)</td>
</tr>
<tr>
<td>Oesophageal/stomach</td>
<td>Hanse n (1998)</td>
<td>Dyspepsia</td>
<td>1 (0.4-2.2)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Heikki nen (1995)</td>
<td>Dyspepsia</td>
<td>0.5 (0.09-2)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Jaskiewicz (1991)</td>
<td>Dyspepsia</td>
<td>0 (0-0.8)</td>
</tr>
<tr>
<td>Oesophageal/stomach</td>
<td>Kagevi (1989)</td>
<td>Dyspepsia</td>
<td>0 (0-2.7)</td>
</tr>
<tr>
<td>Oesophageal</td>
<td>Meineche-Schmidt (2002)</td>
<td>Dyspepsia</td>
<td>0.54 (0.25-1.1)</td>
</tr>
</tbody>
</table>
### The following results are any extra analyses reported by the studies included in the above meta-analysis:

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of Dyspepsia</th>
<th>Age Group</th>
<th>Prevalence (95% CI)</th>
<th>Follow-up</th>
<th>Mean Age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>All patients</td>
<td>0.1 (0.03-0.35)</td>
<td>both</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>Oesophageal Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>Patients ≥ 45 years old</td>
<td>0.18 (0.03-0.71)</td>
<td>both</td>
<td>45</td>
<td>70</td>
</tr>
<tr>
<td>Oesophageal Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>Patients ≥ 50 years old</td>
<td>0.24 (0.04-1)</td>
<td>both</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Oesophageal Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>Patients ≥ 55 years old</td>
<td>0.18 (0.01-1.16)</td>
<td>both</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>Oesophageal Vakil (2009)</td>
<td>Dyspepsia without alarm symptoms</td>
<td>Patients ≥ 60 years old</td>
<td>0.3 (0.02-2)</td>
<td>both</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Oesophageal Hanse (1998)</td>
<td>Ulcer-like dyspepsia</td>
<td>All patients</td>
<td>0.6 (0.03-3.9)</td>
<td>both</td>
<td>Mean age (SD) = 47 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Oesophageal Hanse (1998)</td>
<td>Dysmotility-like dyspepsia</td>
<td>All patients</td>
<td>0 (0-2.9)</td>
<td>both</td>
<td>Mean age (SD) = 47 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Oesophageal Hanse (1998)</td>
<td>Reflux-like dyspepsia</td>
<td>All patients</td>
<td>1.16 (0.2-4.6)</td>
<td>both</td>
<td>Mean age (SD) = 47 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Oesophageal Hanse (1998)</td>
<td>Unclassifiable dyspepsia</td>
<td>All patients</td>
<td>0.9 (0.05-5.8)</td>
<td>both</td>
<td>Mean age (SD) = 47 (16.8)</td>
<td></td>
</tr>
</tbody>
</table>
### META-ANALYSES (2) Stomach

<table>
<thead>
<tr>
<th>Oesophageal/stomach</th>
<th>Meta-analysis</th>
<th>Dyspepsia</th>
<th>All patients</th>
<th>0.65 (0.33-1.3)</th>
<th>both</th>
<th>2 studies &gt; 15, 2 studies &gt; 18, 1 study &gt; 40, 1 study 17-80, 2 studies 18-70, 1 study 19-87, 1 study 18-65, 1 study NR but mean (SD) = 41-42 (15-16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>2 combination gastro-oesophageal and 9 reporting on stomach cancer separately</td>
<td>205x119</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**The 11 studies below are those included in the meta-analysis reported in the cell above (Please note the same data from Hansen (1998) and Meineche-Schmidt (2002) appear both here and under oesophageal, avoid double counting it):**

<table>
<thead>
<tr>
<th>Stomach</th>
<th>Brignoli (1997)</th>
<th>Dyspepsia</th>
<th>All patients</th>
<th>0.4 (0.09-1.14)</th>
<th>both</th>
<th>Mean (SD) age = 41-42 (15-16) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Duggan (2008)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.27 (0.05-1.1)</td>
<td>both</td>
<td>18-70</td>
</tr>
<tr>
<td>Stomach</td>
<td>Edenholm (1985)</td>
<td>Persistance epigastric pain/ulcer-like dyspepsia</td>
<td>All patients who received an UGI endoscopy</td>
<td>1.2 (0.21-4.77)</td>
<td>both</td>
<td>17-80</td>
</tr>
<tr>
<td>Stomach</td>
<td>Hallissy (1990)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>2.28 (1.76-3)</td>
<td>both</td>
<td>40</td>
</tr>
<tr>
<td>Stomach</td>
<td>Hansen (1998)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>1 (0.4-2.2)</td>
<td>both</td>
<td>Mean age (SD) = 47 (16.8)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Heikkinen (1995)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>1.75 (0.8-3.7)</td>
<td>both</td>
<td>77% were &gt; 44 years.</td>
</tr>
<tr>
<td>Stomach</td>
<td>Jaskiewicz (1991)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>2.7 (1.6-4.5)</td>
<td>both</td>
<td>19-87</td>
</tr>
<tr>
<td>Stomach</td>
<td>Kagevi (1989)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>1.16 (0.2-4.6)</td>
<td>both</td>
<td>16</td>
</tr>
<tr>
<td>Stomach</td>
<td>Meineche-Schmidt (1992)</td>
<td>Dyspepsia</td>
<td>All patients</td>
<td>0.54 (0.25-1.1)</td>
<td>both</td>
<td>18-65+</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Disease</td>
<td>Group</td>
<td>Patients</td>
<td>Lower CI</td>
<td>Upper CI</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>--------------------------</td>
<td>----------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Thomas et al. (2003)</td>
<td></td>
<td>Dyspepsia</td>
<td>All patients</td>
<td></td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Vakil et al. (2009)</td>
<td></td>
<td>Dyspepsia without alarm</td>
<td>All patients</td>
<td></td>
<td>0.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Jaskie et al. (1991)</td>
<td></td>
<td>Dyspepsia</td>
<td>Males</td>
<td></td>
<td>3.4</td>
<td>6</td>
</tr>
<tr>
<td>Jaskie et al. (1991)</td>
<td></td>
<td>Dyspepsia</td>
<td>Females</td>
<td></td>
<td>1.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Hanse et al. (1998)</td>
<td></td>
<td>Ulcer-like dyspepsia</td>
<td>All patients</td>
<td></td>
<td>0.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Hanse et al. (1998)</td>
<td></td>
<td>Dysmotility-like dyspepsia</td>
<td>All patients</td>
<td></td>
<td>0</td>
<td>2.9</td>
</tr>
<tr>
<td>Hanse et al. (1998)</td>
<td></td>
<td>Reflux-like dyspepsia</td>
<td>All patients</td>
<td></td>
<td>1.16</td>
<td>4.6</td>
</tr>
<tr>
<td>Hanse et al. (1998)</td>
<td></td>
<td>Unclassifiable dyspepsia</td>
<td>All patients</td>
<td></td>
<td>0.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Vakil et al. (2009)</td>
<td></td>
<td>Dyspepsia</td>
<td>Patients ≥ 45 years old</td>
<td></td>
<td>0.27</td>
<td>0.84</td>
</tr>
<tr>
<td>Vakil et al. (2009)</td>
<td></td>
<td>Dyspepsia</td>
<td>Patients ≥ 50 years old</td>
<td></td>
<td>0.36</td>
<td>1.15</td>
</tr>
<tr>
<td>Vakil et al. (2009)</td>
<td></td>
<td>Dyspepsia</td>
<td>Patients ≥ 55 years old</td>
<td></td>
<td>0</td>
<td>0.86</td>
</tr>
</tbody>
</table>
alarm symptoms | old

| Stomach | Vakil (2009) | Dyspepsia without alarm symptoms | Patients ≥ 60 years old | 0 (0-1.47) | both | 60 | 70 |

**META-ANALYSES (3) Colorectal**

| Colorectal | 1 study from 15, 1 study from 18-65+ and 1 study from 40. | Meta-analysis | Dyspepsia | All patients | 0.6 (0.27-1.35) | both | 15-18 | 65+ |

The 3 studies below are those included in the meta-analysis reported in the cell above:

<table>
<thead>
<tr>
<th>Colorectal</th>
<th>Hallissey (1990)</th>
<th>Dyspepsia</th>
<th>All patients</th>
<th>0.5 (0.3-0.9)</th>
<th>both</th>
<th>40</th>
<th>No upper limit</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Colorectal</th>
<th>Heikkinen (1995)</th>
<th>Dyspepsia</th>
<th>All patients</th>
<th>0 (0-1.2)</th>
<th>both</th>
<th>---</th>
<th>---</th>
</tr>
</thead>
</table>

| Colorectal | Meineche-Schmidt (2002) | Dyspepsia | All patients | 1.14 (0.7-1.9) | both | 18 | 65+ |

**Evidence statement(s):**

Dyspepsia (11 studies, N = 18464) presenting in a primary care setting is associated with an overall positive predictive value of 2.02% for cancer. The study was associated with 1-3 bias/applicability concerns (see also Table 1).

**Evidence tables**

Brignoli (1997)

**PATIENT SELECTION**

A. risk of bias

Patient sampling: Prospective patient series from Switzerland.

Was a consecutive or random sample of patients enrolled? **Unclear**

Was a case-control design avoided? **Yes**

Did the study avoid inappropriate exclusions? **Unclear**

Could the selection of patients have introduced bias? **Unclear risk**
<table>
<thead>
<tr>
<th>B. Concerns regarding applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>Inclusion criteria: “Adult patients with epigastric complaints were admitted to the multicentre [omega]-project if their symptoms persisted for over 1 month and their clinical history and appearance did not suggest an organic disorder (i.e. absence of alarm features, such as gastrointestinal blood loss, palpable tumour mass, massive weight loss, etc.). The studies were conducted by general practitioners acting as primary care physicians.”</td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
</tr>
<tr>
<td>Clinical setting: Primary care, Switzerland</td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric complaints (dyspepsia)</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy and 84-day follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients are accounted for</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
</tr>
</tbody>
</table>

**NOTES**

3 patients had gastric cancer, 0 patients had oesophageal cancer, and 2 patients had cancer outside the digestive tract.
### Duggan (2008)

#### PATIENT SELECTION

**A. risk of bias**

**Patient sampling**  Prospective patient series from 43 GP practices in the UK.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

| N = 762; 411 men, 351 women; mean (range) age = 42 (18-73) years. |

**Inclusion criteria:** Patients aged 18-70 with dyspepsia thought by the GP to arise from the upper GI tract and of sufficient severity to justify empirical treatment with an H$_2$ antagonist or PPI.

**Exclusion criteria:** Patients thought to be unfit for investigation, with alarm symptoms suggestive of malignancy (dysphagia, weight loss > 5 g, anaemia, haematemesis, melaena or jaundice), previous radiological or endoscopic diagnosis of peptic ulcer disease or reflux oesophagitis, investigation for dyspepsia in the previous 5 years with either procedure or symptom onset within 6 months of commencement of NSAID therapy, previous H. pylori eradication therapy or more than 3 prescriptions for acid suppression therapy in the previous 6 months.

**Clinical setting:** Primary care, UK

| Are there concerns that the included patients and setting do not match the review question? | Low concern |

#### INDEX TEST

**A. Risk of bias**

**Index test**  Dyspepsia

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

#### REFERENCE STANDARD

**A. risk of bias**

**Reference standard(s)**  Endoscopy and 1-2-year follow up.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined | Low concern |
### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>At 12-month follow up GP data were available for 753/762.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

2 patients had gastric cancer, 2 patients had oesophageal cancer (the authors report that these patients should not have been included as they had a history of dysphagia).

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from the Distric General Clinic in Huskvarna, Sweden.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 187; 96 men, 91 women; mean/median (range) age = 44 (17-80) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients who between November 1982 and June 1984 called on the clinic because of abdominal pain and who were diagnosed by the general practitioner as having ulcer-like dyspepsia. The criterion used was persistent epigastric pain. Most patients also had additional symptoms such as acid regurgitation, nausea, belching or vomiting.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Sweden</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Ulcer-like dyspepsia. The criterion used was persistent epigastric pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

### REFERENCE STANDARD

**A. risk of bias**

| Reference | UGI endoscopy |

**Edenholm (1985)**

**PATIENT SELECTION**

**A. risk of bias**

**Patient sampling**

Prospective patient series from the Distric General Clinic in Huskvarna, Sweden.

| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Unclear |
| Could the selection of patients have introduced bias? | Unclear risk |

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 187; 96 men, 91 women; mean/median (range) age = 44 (17-80) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria: Patients who between November 1982 and June 1984 called on the clinic because of abdominal pain and who were diagnosed by the general practitioner as having ulcer-like dyspepsia. The criterion used was persistent epigastric pain. Most patients also had additional symptoms such as acid regurgitation, nausea, belching or vomiting.</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: None listed</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: GPs in Sweden</td>
<td></td>
</tr>
</tbody>
</table>

| Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Ulcer-like dyspepsia. The criterion used was persistent epigastric pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. risk of bias**

| Reference | UGI endoscopy |
| standard(s) |  
| Is the reference standard likely to correctly classify the target condition? | Yes |
| | Were the reference standard results interpreted without knowledge of the results of the index tests? | No |
| | Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

| A. risk of bias |  
| Flow and timing | 20/187 patients declined endoscopy and it was unsuccessful in a further 2 patients. Thus the PPV is likely to be an over-estimate, calculated as 2/165. |
| | Was there an appropriate interval between index test and reference standard? | Yes probably |
| | Did all patients receive the same reference standard? | Yes |
| | Were all patients included in the analysis? | No |
| | Could the patient flow have introduced bias? | High risk |

**NOTES**

There were a total of 3 cancers confirmed in the 165 patients who received UGI endoscopy: 1 oesophageal cancer, 1 stomach cancer, and 1 cancer of the duodenum, the latter of which was included with the stomach cancer.

Hallissey (1990)

**PATIENT SELECTION**

| A. risk of bias |  
| Patient sampling | Propective consecutive patient series from a group of 10 general practices in England. |
| | Was a consecutive or random sample of patients enrolled? | Yes |
| | Was a case-control design avoided? | Yes |
| | Did the study avoid inappropriate exclusions? | Yes |
| | Could the selection of patients have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Patient characteristics and setting | N = 2585 aged > 40 years. No other information reported. The patient group was equally divided between new patients with dyspepsia, old patients with uninvestigated dyspepsia, and old patients with investigated dyspepsia. |
| | Inclusion criteria: All patients over 40 years making their first attendance during the study period (4 years and 9 months) with any degree of dyspepsia |
| | Exclusion criteria: None listed. |
| | Clinical setting: Primary care, England. |
| | Are there concerns that the included patients and setting do not match the review question? | Unclear concern |

**INDEX TEST**

| A. Risk of bias |  
| Index test | Dyspepsia of any degree |
Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

REFERENCE STANDARD

A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 4 weeks and follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

FLOW AND TIMING

A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>2659 patients were seen and 2585 attended for investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

NOTES

Malignancy was detected in 115 patients: Gastric adenocarcinoma (57), gastric lymphoma (1; added to the gastric adenocarcinoma data in the PPV), oesophageal cancer (15), colorectal (14), pancreatic (6), bronchial (8), prostatic (2), duodenal (1, also added to the gastric carcinoma data in the PPV), liver (1), gall bladder (1), carcinoid (1), uterine (1), leukaemia (1), carcinomatosis of unknown primary (7).

Hansen (1998)

PATIENT SELECTION

A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series from general an open-access endoscopy clinic in Denmark.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

B. Concerns regarding applicability

| Patient | N = 612 from 66 GPs; 288 males / 324 females; mean age (SD) = 47 (16.8) |
Inclusion criteria: “All general practitioners (n = 108) in the city of Odense (population, 170,000) were invited to participate in the study. GPs were asked to refer all patients who consulted them with dyspepsia, regardless of the severity of the symptoms. To obtain compliance with this request the participating GPs were sent numerous reminders. Because of a limited endoscopy capacity not all GPs took part in the study at the same time.“Study period was 11 March 1991-27 March 1992.

Exclusion criteria: Aged < 18 years, signs of UGI bleeding, abdominal emergency, jaundice, previous surgery in the UGI tract except for closure of an ulcer, supposed acute bacterial or viral infection, pregnancy, or endoscopy contraindicated.

Clinical setting: GPs in Denmark

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

Epigastric or retrosternal pain or discomfort, with or without heartburn, nausea, vomiting, and any other symptom considered to be referable to the proximal alimentary tract.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**

Endoscopy within 1 week of referral and follow up

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
</tbody>
</table>

| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>56 eligible patients declined participation. These patients were older than the study group (mean age = 52 years versus 47 years) and they were characterised by a shorter dyspepsia history (median duration = 1 month, range = 4 days to 35 years versus 2 months, range = 4 days to 14 years). Fewer of the non-participating patients had had a previous endoscopy or UGI</th>
</tr>
</thead>
</table>
radiography (22% versus 43%, but identical proportions of the patients had an ulcer history (11% versus 14%).

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

There were a total of 4 cancers histologically confirmed in the study. No subclassification of the cancers reported. Follow up of the 364 patients with normal endoscopy revealed missing date in 5% of the cases and 1 lymphoma and 1 rectal carcinoma. These 6 cancers (NOS) are included in the overall PPV for dyspepsia.

Heikkinen (1995)

**PATIENT SELECTION**

**A. risk of bias**

**Patient sampling**

Consecutive patient series from 11 GPs (from 3 rural health centres) and from the catchment area of 6 physicians in the health centre of an urban area (population [individuals > 14 years old] of study area = 24600) in Finland.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Patient characteristics and setting**

N = 400; 152 males, 248 females; 77% were > 44 years.

Inclusion criteria: Consecutive patients who consulted their GP from January 11th 1993 to January 12th 1994 for dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

Exclusion criteria: Patients with symptoms of an acute condition within the abdomen or who had had an upper intestinal endoscopy performed within the last 3 months or aged < 15 years.

Clinical setting: Primary care, Finland.

**Are there concerns that the included patients and setting do not match the review question?**

Unclear concern

**INDEX TEST**

**A. Risk of bias**

**Index test**

Dyspepsia (defined as upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to be referable to the proximal alimentary tract).

<table>
<thead>
<tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

**Are there concerns that the index test, its conduct, or the reference standard do not match the review question?**

Low concern
### Interpretation differ from the review question?

**REFERENCE STANDARD**

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy, upper abdominal ultrasound, more detailed interview, blood count, serum screening (creatinine, alkaline phosphatise, alanine aminotransferase, amylase, and C-reactive protein), lactose intolerance test, and follow up of ≥ 1 month.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

In total N = 9 had cancer: 0 colorectal, 2 oesophageal and 7 stomach (of which 3 were lymphomas of the MALT type (Mucosa-associated lymphoid tissue).

Jaskiewicz (1991)

### PATIENT SELECTION

#### A. risk of bias

| Patient series from a program aimed at screening patients with chronic gastric complaints for gastric carcinoma in the South and North-Western Cape Province of South Africa. |
| Patient series from a program aimed at screening patients with chronic gastric complaints for gastric carcinoma in the South and North-Western Cape Province of South Africa. |
| Was a consecutive or random sample of patients enrolled? | Unclear |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Unclear |
| Could the selection of patients have introduced bias? | Unclear risk |

#### B. Concerns regarding applicability

| Patient characteristics and setting | N = 585, 355 males, 230 females; mean (range) age males = 45.1 (19-87) years, mean (range) age females = 47.2 (19-87) years. |
| Inclusion criteria: “participants who were treated for dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months. Patients represented various areas in the south-and north-western Cape province including Namaqualand, and formed part of a programme aimed at screening patients with chronic |
| Unclear |
| Yes |
| Unclear |
gastric complaints for gastric carcinoma.”
Exclusion criteria: None listed
Clinical setting: Unclear, South Africa.

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Unspecified dyspepsia (dyspeptic complaints such as epigastric pain, heartburn, post-prandial pain and bloating, vomiting or nausea with a duration of at least 3 months).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Unclear concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Endoscopy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

In total N = 16 had gastric cancer. No oesophageal cancers reported.

Kagevi (1989)

**PATIENT SELECTION**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Propective consecutive patient series from a primary care centre in Sweden.</th>
</tr>
</thead>
</table>

<p>| Was a consecutive or random sample of patients enrolled? | Yes |</p>
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics and setting</td>
<td>N = 172; 88 men, 84 women; mean (SD) age = 43 (16) years.</td>
</tr>
<tr>
<td>Inclusion criteria: “All patients visiting the medical center with complaints referable to the digestive tract were considered for inclusion. Even when the patient consulted the primary care center because of another complaint and coincidentally mentioned gastrointestinal problem, the patient was considered for inclusion. The patient’s gastrointestinal problem could have been reported in connection with an earlier visit at the primary care center.”</td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Patients with jaundice, gastrointestinal bleeding or acute abdominal pain were excluded and so were patients judged to have a non-gastro-enterologic cause of their symptoms (gynaecologic problems, spondylosis deformans, etc), patients aged &lt; 16 years and patients unwilling to participate.</td>
<td></td>
</tr>
<tr>
<td>Clinical setting: Primary care Center, Sweden.</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Unclear concern</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>Dyspepsia defined as any pain, discomfort, or other symptoms referable to the digestive tract ≥ 2 weeks. Symptoms could be intermittent or continuous.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Esophagogastroduodenoscopy withion 1 week and 6 month follow up.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>13/185 patients were excluded as they did not want to have an endoscopy</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**
2 patients had gastric cancer, 0 patients had oesophageal cancer.

**Meineche-Schmidt (2002)**

**PATIENT SELECTION**

**A. risk of bias**

Patient sampling: Consecutive patient series from 82 GPs in Denmark.

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of patients have introduced bias? Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting: N = 1491; 688 males, 803 females; age groups: 18-37 years: N = 377; 38-50 years: N = 369; 51-64 years: N = 338; 65- years: N = 402.

Inclusion criteria: Consecutive patients who consulted their GP between June 1991 and May 1993 for dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).

Exclusion criteria: None listed.

Clinical setting: Primary care, Denmark.

Are there concerns that the included patients and setting do not match the review question? Unclear concern

**INDEX TEST**

**A. Risk of bias**

Index test: Dyspepsia (defined as pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract).

Were the index test results interpreted without knowledge of the results of the reference standard? Yes

Could the conduct or interpretation of the index test have introduced bias? Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern

**REFERENCE STANDARD**

**A. risk of bias**

Reference standard(s): 18 months-3 years and 10 months follow up.

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index tests? No

Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk
### B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**  
**Low concern**

### FLOW AND TIMING

**A. risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients appear to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was there an appropriate interval between index test and reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did all patients receive the same reference standard?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Were all patients included in the analysis?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the patient flow have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

In total N = 31 had cancer: 17 colorectal, 8 gastro-oesophageal (no subgroup analyses presented for these patients) and 6 other.

---

**Thomson (2003)**

### PATIENT SELECTION

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Propective patient series from a group of 49 family physician practices in Canada.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Was a consecutive or random sample of patients enrolled?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Was a case-control design avoided?</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Did the study avoid inappropriate exclusions?</strong></td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the selection of patients have introduced bias?</strong></td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 1040, 520 males / 520 females; mean (range) age =45.6 (18-84) years.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td>Patients ≥ 18 years with a primary complaint of ≥ 3 months intermittent or continuous dyspepsia. Patients could not have used proton pump inhibitors within 30 days or prokinetics or prescription H₂-receptor antagonists (H₂RAS) within 14 days of enrolment.</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td>Heartburn or acid regurgitation as their sole symptom; documented history of upper GI pathology/surgery; clinical investigation of dyspepsia by endoscopy or radiology in the previous 6 months or more than twice in the past 10 years; H. pylori eradication treatment in the previous 6 months; irritable bowel syndrome as assessed by the presence of ≥ manning criteria; or severe concurrent disease.</td>
</tr>
<tr>
<td><strong>Clinical setting:</strong></td>
<td>Family physician practice, Canada.</td>
</tr>
</tbody>
</table>

**Are there concerns that the included patients and setting do not match the review question?**  
**Unclear concern**

### INDEX TEST

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>Dyspepsia defined as symptom complex of epigastric pain/discomfort in association with other upper GI symptoms, including heartburn and acid regurgitation.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Were the index test results interpreted without knowledge of the results of the reference standard?</strong></td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Could the conduct or interpretation of the index test have introduced bias?

Low risk

### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Low concern

### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Upper gastrointestinal endoscopy within 10 days and 6-months follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>No</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question?

Low concern

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients are accounted for. 1100/1171 enrolled patients consented to endoscopy, but 60/1100 did not received endoscopy (eligibility criteria not fulfilled [27], lost to follow up [3], withdrew consent [9], non-compliant with the protocol [1], endoscopy-intolerable [2], other [18]).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

Malignancy was detected in 2 patients: Gastric (MALToma; 1), oesophageal cancer (1).

### Vakil (2009)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes (probably)</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>N = 2741, mean (range) age = not reported (not reported) years, numbers of females/males: Not reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria:</td>
<td>Patients aged 18-70 years who met Rome II criteria for dyspepsia (intermittent or continuous pain or burning centered in the upper</td>
</tr>
</tbody>
</table>
abdomen for ≥ 3 months).

**Exclusion criteria:** Past diagnosis of gastro-oesophageal reflux disease, predominant symptom of heartburn or regurgitation, history of heartburn or regurgitation > 2 days/week, treatment > 2 days/week with non-steroidal anti-inflammatory drugs or cyclooxygenase-2 selective inhibitors or aspirin (except for cardiovascular prophylaxis at doses ≤ 325 mg/day), concurrent alarm features (e.g., dysphagia, recurrent vomiting, unexplained anaemia, gastro-intestinal bleeding), H pylori eradication treatment within 12 months, maintenance therapy with either a proton pump or an H2-receptor antagonist within 6 months.

**Clinical setting:** The study was conducted in 190 primary care health centers in 17 countries (Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Greece, Iceland, Italy, Norway, Romania, Singapore, South Africa, Spain, Sweden, Switzerland). Patients were recruited from primary care clinics where flyers publicising the study were placed and the primary care physicians recruited patients presenting to their offices with dyspepsia [random or consecutive sampling unlikely].

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

**Index test**

Dyspepsia/ intermittent or continuous pain or burning centered in the upper abdomen for ≥ 3 months. Symptoms were evaluated using a scale validated in a number of languages

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

**Reference standard(s)**

All patients received outpatient endoscopy

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>No (but all patients had a positive index test)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All the patients are accounted for in the results.</th>
</tr>
</thead>
</table>

<p>| Was there an appropriate interval between index test and reference standard? | Yes (probably) |</p>
<table>
<thead>
<tr>
<th>reference standard?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

Supported by AstraZeneca R&D Sweden. The authors state that “The sponsor did not play any role in the calculations or in the writing of the manuscript”.

Six patients had cancer: 3 oesophagus and 3 stomach.

### References

#### Included studies

WEIGHT LOSS

Risk of bias in the included studies
The risk of bias and applicability concerns are summarised per study in the figure below. The body of evidence was generally of high quality. The main validity issues to note is that patient sampling was not clearly consecutive or random in a number of the studies, and that some of studies suffered from missing data. Studies employing non-consecutive/random sampling are at risk of bias because, for example, case-control studies have been shown to be associated with inflated test accuracy parameters compared to designs that incorporate random or consecutive patient selection. The statistical analyses employed by these studies are however likely to have gone some way in addressing this issue. One study was conducted in a setting that is unlikely to be directly applicable to UK-based primary care and, as a consequence, also seems to present inflated PPVs that may be more reflective of secondary care. Finally, some of the studies were compromised by missing data, the influence of which on the results is difficult to determine.

![Risk of Bias Diagram](image)

Table 1: Non-site specific symptoms of concern: Calculation of overall positive predictive value of weight loss for cancer
<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Study</th>
<th>Lower age limit</th>
<th>Upper age limit</th>
<th>PPV (95% CI), prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/renal</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.41 (0.3-0.6)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Meta-analysis</td>
<td>18</td>
<td>87</td>
<td>3 (0.32-22.89)</td>
</tr>
<tr>
<td>Lung</td>
<td>Hamilton (2005)</td>
<td>40</td>
<td>No upper limit</td>
<td>1.1 (0.8-1.6)</td>
</tr>
<tr>
<td>Oesophagus/stomach</td>
<td>Hippisley-Cox (2011)</td>
<td>30</td>
<td>84</td>
<td>1.2 (1-1.4)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Hippisley-Cox (2012)</td>
<td>30</td>
<td>84</td>
<td>0.6 (0.5-0.8)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Hamilton (2006)</td>
<td>40</td>
<td>No upper limit</td>
<td>0.75 (0.38-1.4)</td>
</tr>
<tr>
<td>Sum</td>
<td></td>
<td></td>
<td></td>
<td>7.06</td>
</tr>
</tbody>
</table>

**Table 2: Non-site specific symptoms of concern: Positive predictive values for weight loss**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Comment/relev ant recs</th>
<th>Study</th>
<th>Symptom</th>
<th>Patient group</th>
<th>Positive predictive value% (95% CI)</th>
<th>Sex</th>
<th>Age inclusion, lower limit</th>
<th>Age inclusion, upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Collins (2013a)</td>
<td>Weight loss</td>
<td>Woman</td>
<td>0.1 (0.1-0.2)</td>
<td>Women</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Bladder/renal</td>
<td></td>
<td>Hippisley-Cox (2012b)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.41 (0.3-0.6)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Hamilton (2005a)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>1.1 (0.8-1.6)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Hamilton (2005a)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>1.2 (0.7-2.3)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Hamilton (2005a)</td>
<td>Weight loss</td>
<td>All smokers</td>
<td>2.1 (NR)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Hamilton (2005a)</td>
<td>Weight loss</td>
<td>All smokers</td>
<td>1.7 (NR)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>Iyen-Omonofo man (2013)</td>
<td>Weight loss</td>
<td>Validation cohort</td>
<td>0.34 (0.23-0.5)</td>
<td>both</td>
<td>40</td>
<td>no upper limit</td>
</tr>
<tr>
<td>Oesophagus/stomach</td>
<td></td>
<td>Collins (2012a)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.8 (0.7-0.9)</td>
<td>both</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Tumor Type</td>
<td>Study</td>
<td>Outcome Measure</td>
<td>Study Population</td>
<td>Women</td>
<td>Men</td>
<td>Age Range</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Oesophagus/Stomach</td>
<td>Collins (2012a)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.6 (0.4-0.7)</td>
<td>Women</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus/Stomach</td>
<td>Collins (2012a)</td>
<td>Weight loss</td>
<td>Men</td>
<td>1 (0.9-1.2)</td>
<td>Men</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus/Stomach</td>
<td>Hippisley-Cox (2011)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>1.2 (1-1.4)</td>
<td>both</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Collins (2013)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.28 (0.22-0.35)</td>
<td>both</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Collins (2013)</td>
<td>Weight loss</td>
<td>Women</td>
<td>0.16 (0.11-0.24)</td>
<td>women</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Collins (2013)</td>
<td>Weight loss</td>
<td>Men</td>
<td>0.42 (0.32-0.54)</td>
<td>men</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Hippisley-Cox (2012a)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.6 (0.5-0.8)</td>
<td>both</td>
<td>30-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Stapley (2012)</td>
<td>Weight loss</td>
<td>All patients</td>
<td>0.44 (0.36-0.55)</td>
<td>both</td>
<td>40-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Stapley (2012)</td>
<td>Weight loss</td>
<td>Patients ≥ 60 years</td>
<td>0.8 (0.7-1)</td>
<td>both</td>
<td>60-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Hamilton (2006)</td>
<td>Loss of weight (reported twice)</td>
<td>All patients</td>
<td>2.1 (NR)</td>
<td>men</td>
<td>40-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Hamilton (2006)</td>
<td>Loss of weight (reported once)</td>
<td>All patients</td>
<td>1.2 (0.9-1.6)</td>
<td>both</td>
<td>40-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Loss of weight (reported twice)</td>
<td>All patients</td>
<td>1.4 (0.8-2.6)</td>
<td>both</td>
<td>40-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Loss of weight (reported once)</td>
<td>All patients</td>
<td>0.74 (NR)</td>
<td>both</td>
<td>40-69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Loss of weight (40-69 years)</td>
<td>All patients</td>
<td>2.5 (NR)</td>
<td>both</td>
<td>70-84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal Contact</td>
<td>Hamiton (2005)</td>
<td>Weight Loss</td>
<td>Age Range</td>
<td>Hazard Ratio (95% CI)</td>
<td>Sex</td>
<td>Age Range</td>
<td>Hazard Ratio (95% CI)</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Men aged &lt; 60 years</td>
<td>0.1 (0.05-0.2)</td>
<td>Males</td>
<td>40</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Men aged 60-69 years</td>
<td>0.3 (0.2-0.4)</td>
<td>Males</td>
<td>60</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Men aged 70-79 years</td>
<td>0.7 (0.5-0.8)</td>
<td>Males</td>
<td>70</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Men aged ≥ 80 years</td>
<td>0.3 (0.2-0.4)</td>
<td>Males</td>
<td>80</td>
<td>no upper limit</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Men &lt; 60 years</td>
<td>0.2 (0.1-0.3)</td>
<td>Males</td>
<td>40</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Men 60-69 years</td>
<td>0.7 (0.4-0.9)</td>
<td>Males</td>
<td>60</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Men 70-79 years</td>
<td>1.5 (1.2-1.8)</td>
<td>Males</td>
<td>70</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Men ≥ 80 years</td>
<td>0.8 (0.6-1.4)</td>
<td>Males</td>
<td>80</td>
<td>no upper limit</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Women &lt; 60 years</td>
<td>0.05 (0.05-0.05)</td>
<td>Females</td>
<td>40</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td></td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Women 60-69 years</td>
<td>0.2 (0.1-0.3)</td>
<td>Females</td>
<td>60</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Meta-analysis</td>
<td>Weight loss</td>
<td>All patients</td>
<td>Odds Ratio</td>
<td>Sex</td>
<td>Age Range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Wome n 70-79 years</td>
<td>0.4 (0.3-0.6)</td>
<td>Females</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss 5-10% (read off graph)</td>
<td>Wome n ≥ 80 years</td>
<td>0.4 (0.3-0.6)</td>
<td>Females</td>
<td>80</td>
<td>no upper limit</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Wome n &lt; 60 years</td>
<td>0.06 (0.06-0.08)</td>
<td>Females</td>
<td>40</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Wome n 60-69 years</td>
<td>0.5 (0.3-0.7)</td>
<td>Females</td>
<td>60</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Wome n 70-79 years</td>
<td>0.8 (0.6-1.1)</td>
<td>Females</td>
<td>70</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hamilton (2005)</td>
<td>Weight loss ≥ 10% (read off graph)</td>
<td>Wome n ≥ 80 years</td>
<td>0.8 (0.6-1.1)</td>
<td>Females</td>
<td>80</td>
<td>no upper limit</td>
<td></td>
</tr>
</tbody>
</table>

**META-ANALYSES (1) Colorectal**

The 3 studies below are those included in the meta-analysis reported in the cell above:

<table>
<thead>
<tr>
<th>Study</th>
<th>Meta-analysis</th>
<th>Weight loss</th>
<th>All patients</th>
<th>Odds Ratio</th>
<th>Sex</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Collins (2012)</td>
<td>Weight loss</td>
<td>Males</td>
<td>0.8 (0.7-0.9)</td>
<td>both</td>
<td>30</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Hippisley-Cox (2012)</td>
<td>Weight loss</td>
<td>Males</td>
<td>0.8 (0.7-0.9)</td>
<td>both</td>
<td>30</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Panzuto (2003)</td>
<td>Weight loss</td>
<td>Males</td>
<td>35.7 (22-52)</td>
<td>both</td>
<td>18</td>
</tr>
</tbody>
</table>

The following results are any extra analyses reported by the studies included in the above meta-analysis:

<table>
<thead>
<tr>
<th>Study</th>
<th>Meta-analysis</th>
<th>Weight loss</th>
<th>Males</th>
<th>Odds Ratio</th>
<th>Females</th>
<th>Odds Ratio</th>
<th>Sex</th>
<th>Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Collins (2012)</td>
<td>Weight loss</td>
<td>Females</td>
<td>0.6 (0.5-0.7)</td>
<td>Females</td>
<td>30</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>
Evidence statement(s):

Weight loss (8 studies, N = 3768550) presenting in a primary care setting is associated with an overall positive predictive value of 7.06% for cancer. The studies were associated with 0-3 bias/applicability concerns (see also Table 1).

Evidence tables

Collins (2012)

<table>
<thead>
<tr>
<th>PATIENT SELECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
</tr>
<tr>
<td>Patient sampling</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics and setting</td>
</tr>
<tr>
<td>A total of 2135540 patients were identified from 364 practices.</td>
</tr>
<tr>
<td>Symptoms:Rectal bleeding (N = 56234; 28423 men, 27811 women), abdominal pain (N = 245989; 102192 men, 143797 women), appetite loss (N = 5776; 2481 men, 3295 women), weight loss (N = 28289; 12891 men, 15398 women), anaemia (N = 18125; 4466 men, 13659 women), change in bowel habit (men only, N = 1670).</td>
</tr>
<tr>
<td>Incident cases of colorectal cancer during the 2-year follow up period: N = 3712 (2036 men, 1676 women).</td>
</tr>
<tr>
<td>Inclusion criteria:Patients aged 30-84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.</td>
</tr>
<tr>
<td>Exclusion criteria:Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.</td>
</tr>
<tr>
<td>Clinical setting: Primary care, UK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>INDEX TEST</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Risk of bias</strong></td>
</tr>
<tr>
<td>Index test</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there concerns that the index test, its conduct, or</td>
</tr>
</tbody>
</table>
### REFERENCE STANDARD

#### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients seem to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### NOTES

The is very large, if not complete, overlap of the data used in this study with those used in Hamilton (2008 [for anaemia], 2009)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Retrospective patient series using the THIN database.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | A total of 2135540 patients were identified from 364 practices. Symptoms: Dysphagia (N = 19237; 8846 men, 10391 women), abdominal pain (N = 246998; 102732 men, 144266 women), appetite loss (N = 5838; 2521 men, 3317 women), weight loss (N = 28403; 1293 men, 15465 women), haematemesis (N = 10792; 6162 men, 4630 women), anaemia (N = 18355; 4563 men, 13792 women). Incident cases of gastro-oesophageal cancer during the 2-year follow up period: N = 1766 (1184 men, 582 women; 32% gastric cancer, 68% oesophageal cancer). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January |

Collins (2012a)
2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.

Exclusion criteria: Patients with a prior diagnosis of gastro-oesophageal cancer, registration with the general practice < 12 months, or with invalid dates.

Clinical setting: Primary care, UK

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

A. Risk of bias


| Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
| Could the conduct or interpretation of the index test have introduced bias? | Low risk |

B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |

**REFERENCE STANDARD**

A. Risk of bias

Reference standard(s): 2-year follow up

| Is the reference standard likely to correctly classify the target condition? | Yes |
| Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
| Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

**FLOW AND TIMING**

A. Risk of bias

Flow and timing: All patients seem to be accounted for

| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| Could the patient flow have introduced bias? | Low risk |

**NOTES**

The study did not distinguish between gastric and oesophageal cancer

Collins (2013)

**PATIENT SELECTION**

A. Risk of bias
Patient sampling | Retrospective patient series using the THIN database.
---|---
Was a consecutive or random sample of patients enrolled? | Yes
Was a case-control design avoided? | Yes
Did the study avoid inappropriate exclusions? | Yes
Could the selection of patients have introduced bias? | Low risk

**B. Concerns regarding applicability**

Patient characteristics and setting | A total of 2150322 patients were identified from 364 practices. Symptoms: Dysphagia (men only: N = 9326), abdominal pain (N = 255058; 106768 men, 148290 women), appetite loss (N = 6102; 2658 men, 3444 women), weight loss (N = 29464; 13484 men, 15980 women), abdominal distension (women only: N = 4457), constipation (men only, N = 5326).
Incident cases of pancreatic cancer during the 2-year follow up period: N = 287 (331 men, 287 women).

Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period.
Exclusion criteria: Patients with a prior diagnosis of pancreatic cancer, registration < 12 months with the general practice, or invalid dates.
Clinical setting: Primary care, UK

Are there concerns that the included patients and setting do not match the review question? | Low concern

**INDEX TEST**

A. Risk of bias

**Index test** | ‘Red-flag’ symptoms: Dysphagia (men only), loss of appetite, weight loss, abdominal pain, abdominal distension (women only), and constipation (men only).

Were the index test results interpreted without knowledge of the results of the reference standard? | Yes
Could the conduct or interpretation of the index test have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern

**REFERENCE STANDARD**

A. Risk of bias

Reference standard(s) | 2-year follow up

Is the reference standard likely to correctly classify the target condition? | Yes
Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear

Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk

**B. Concerns regarding applicability**

Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern
--- | ---
**FLOW AND TIMING**

A. **risk of bias**

| Flow and timing | All patients seem to be accounted for |
| Was there an appropriate interval between index test and reference standard? | Yes |
| Did all patients receive the same reference standard? | Yes |
| Were all patients included in the analysis? | Yes |
| Could the patient flow have introduced bias? | Low risk |

**NOTES**

Collins (2013a)

**PATIENT SELECTION**

A. **risk of bias**

| Patient sampling | Retrospective patient series using the THIN database. |
| Was a consecutive or random sample of patients enrolled? | Yes |
| Was a case-control design avoided? | Yes |
| Did the study avoid inappropriate exclusions? | Yes |
| Could the selection of patients have introduced bias? | Low risk |

**B. Concerns regarding applicability**

| Patient characteristics and setting | A total of 2145133 patients (1063355 men, 1081778 women) were identified from 364 practices. Symptoms: Haemoglobin < 11 g/dl recorded in the last year (N = 16961; 3969 men, 12992 women), abdominal pain (N = 253344; 105247 men, 148097 women), appetite loss (N = 6097; 2616 men, 3481 women), weight loss (N = 29369; 13332 men, 16037 women), haematuria (N = 37810; 22810 men, 15000 women), previous diagnosis of cancer apart from renal tract cancer at study entry (N = 49303; 18130 men, 31173 women). Incident cases of renal tract cancer during the 2-year follow up period: N = 2283 (1685 men, 598 women). Inclusion criteria: Patients aged 30–84 years and registered with practices between 1 January 2000 and 30 June 2008. Entry to the cohort was defined as the latest of the study start date; the date the patient registered with the practice; and for those patients with red flag symptoms (e.g., haematuria, abdominal pain, weight loss, appetite loss, and anaemia), the date of the first recorded onset within the study period. Exclusion criteria: Patients with a prior diagnosis of renal tract cancer, registered less than 12 months with the general practice, had invalid dates, < 30 years old or ≥ 85 years old. Clinical setting: Primary care, UK |

**Are there concerns that the included patients and setting do not match the review question?** | Low concern

**INDEX TEST**

A. **Risk of bias**

| Index test | ‘Red-flag’ symptoms were defined as symptoms that might alarm the patient |
and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation have introduced bias from the review question?</td>
<td>Low concern</td>
</tr>
</tbody>
</table>

**REFERENCE STANDARD**

A. Risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes. Patients without the outcome were censored at the earliest of the date of death, date of leaving the practice study of 2 years of follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

| B. Concerns regarding applicability                                      |         |
| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern|

**FLOW AND TIMING**

A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>All patients seem to be accounted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

It is unclear why no data has been presented for men for the symptoms of appetite loss and weight loss.

**Hamilton (2005)**

**PATIENT SELECTION**

A. Risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## For diagnostic case-control studies:
The groups were comparable at baseline, including all major confounding and prognostic factors?

| Yes |

| **Could the selection of patients have introduced bias?** |
| High risk |

## B. Concerns regarding applicability

### Patient characteristics and setting

**Cases:**
- N = 349 (177 males/172 females), age at diagnosis: < 60 years: N = 45, 60-69 years: N = 97, 70-79 years: N = 113, 80+ years: N = 94. 210/349 had tumours at or distal to the splenic flexure, and 126/349 had tumours proximal to the splenic flexure, the remaining 13/349 has tumours in multiple or unknown sites. Duke's staging was known for 305/349: 170/305 were Duke's A or B, and 135/305 were Duke's C or D.

**Controls:**
- N = 1744 (885 males/859 females), age at diagnosis: < 60 years: N = 225, 60-69 years: N = 487, 70-79 years: N = 555, 80+ years: N = 477.

**Inclusion criteria:**
- Cases: All patients aged ≥ 40 years with a primary colorectal cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register.
- Controls: Five controls were matched to each case on sex, general practice, and age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case.

**Exclusion criteria:**
- Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous colorectal cancer; or residence outside Exeter at the time of diagnosis.

**Clinical setting:** Primary care, UK.

### Are there concerns that the included patients and setting do not match the review question?

| Low concern |

## INDEX TEST

### A. Risk of bias

**Index test**
- Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

**Were the index test results interpreted without knowledge of the results of the reference standard?**

| Yes |

**For diagnostic case-control studies:**
- Investigators were kept 'blind' to other important confounding and prognostic factors?

| Yes |

**Could the conduct or interpretation of the index test have introduced bias?**

| Low risk |

## B. Concerns regarding applicability

### Are there concerns that the index test, its conduct, or interpretation differ from the review question?

| Low concern |
**REFERENCE STANDARD**

### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Colorectal cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern

**FLOW AND TIMING**

### A. risk of bias

Flow and timing All the patients are accounted for.

| | Was there an appropriate interval between index test and reference standard? | Yes |
| | Did all patients receive the same reference standard? | Yes |
| | Were all patients included in the analysis? | Yes |
| | Could the patient flow have introduced bias? | Low risk |

**NOTES**

Hamilton (2005a)

**PATIENT SELECTION**

### A. risk of bias

Patient sampling Population-based matched case-control study involving all 21 general practices in Exeter, Devon, UK.

| | Was a consecutive or random sample of patients enrolled? | No |
| | Was a case-control design avoided? | No |
| | Did the study avoid inappropriate exclusions? | Yes |

**For diagnostic case-control studies:**

Attempts were made within the design or analysis to balance the comparison groups for potential confounders? Yes

**For diagnostic case-control studies:**

The groups were comparable at baseline, including all major confounding and prognostic factors? Yes

| | Could the selection of patients have introduced bias? | High risk |

### B. Concerns regarding applicability

Patient characteristics and setting

| Cases: | N = 247 (170 males/77 females), age at diagnosis: < 60 years: N = 35, 60-69 years: N = 60, 70-79 years: N = 118, 80+ years: N = 34. |
| Inclusion criteria: | |

Inclusion criteria:
Cases: All patients aged ≥ 40 years with a primary lung cancer, diagnosed from 1998 to 2002, were identified from the cancer registry at the Royal Devon and Exeter Hospital combined with computerised searches at every practice in Devon to identify any cases missing from the cancer register. Controls: Five controls were matched to each case on sex, general practice, and age. Controls were eligible if they were alive at the time of diagnosis of their case.

Exclusion criteria:
Cases and controls: Unobtainable records; no consultations in the 2 years before diagnosis; previous lung cancer; or residence outside Exeter at the time of diagnosis.

Clinical setting: Primary care, UK.

### Are there concerns that the included patients and setting do not match the review question?

| Low concern |

### INDEX TEST

#### A. Risk of bias

**Index test**
Anonymised photocopies of the full primary care records for 2 years before diagnosis were coded (blinded to case/control status) for all entries using the International Classification of Primary Care-2. Additional codes were created to incorporate all possible clinical features. Only variables occurring in ≥ 2.5% of cases or controls were analysed.

**Were the index test results interpreted without knowledge of the results of the reference standard?**
Yes

**For diagnostic case-control studies:**
Investigators were kept 'blind' to other important confounding and prognostic factors?
Yes

**Could the conduct or interpretation of the index test have introduced bias?**
Low risk

### B. Concerns regarding applicability

| Low concern |

### REFERENCE STANDARD

#### A. risk of bias

**Reference standard(s)**
Lung cancer diagnosis in the cancer registry at the Royal Devon and Exeter Hospital or practice notes.

**Is the reference standard likely to correctly classify the target condition?**
Yes

**Were the reference standard results interpreted without knowledge of the results of the index tests?**
Unclear

**Could the reference standard, its conduct, or its interpretation have introduced bias?**
Low risk

### B. Concerns regarding applicability

| Low concern |

### FLOW AND TIMING

#### A. risk of bias

**Flow and timing**
All the patients are accounted for.

**Was there an appropriate interval between index test and**
Yes
<table>
<thead>
<tr>
<th>reference standard?</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

**NOTES**

**Hamilton (2006)**

**PATIENT SELECTION**

**A. risk of bias**

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Population-based case-control study, involving all 21 general practices in Exeter, Devon, UK.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**For diagnostic case-control studies:**

Attempts were made within the design or analysis to balance the comparison groups for potential confounders?

| Yes |

**For diagnostic case-control studies:**

The groups were comparable at baseline, including all major confounding and prognostic factors?

| Yes |

**Could the selection of patients have introduced bias?**

| High risk |

**B. Concerns regarding applicability**

**Patient characteristics and setting**

| Cases: | 217 male patients; age at diagnosis: < 60 years: N = 15 (7%); 60-69 years: N = 51 (24%); 70-79 years: N = 100 (46%); ≥ 80 years: N = 51 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). |
| Controls: | 1080 male patients; age at diagnosis: < 60 years: N = 79 (7%); 60-69 years: N = 253 (23%); 70-79 years: N = 494 (46%); ≥ 80 years: N = 254 (24%); median number of consultations in the 2 years preceding diagnosis = 14 (IQR = 10-21). |

**Inclusion criteria:**

Cases: All patients aged 40 years or over with prostate cancer, diagnosed from 1998 to 2002 inclusive, were identified from the cancer registry at the Royal Devon and Exeter Hospital (the only hospital offering urological services to Exeter patients). Computerised searches at every practice identified any cases missing from the register. Cases without positive histology were included if the records contained a consultant urologist diagnosis of cancer based on strong clinical evidence.

Controls: Five male controls were matched to each case on general practice and on age (to 1-year bands if possible, increased in 1-year multiples to a maximum of 5 years). Controls were eligible if they were alive at the time of diagnosis of their case.

**Exclusion criteria:** Unobtainable records; no consultations in the 2 years before diagnosis; previous prostate cancer; or residence outside Exeter at the time of diagnosis.
<table>
<thead>
<tr>
<th><strong>Clinical setting:</strong> Primary care, UK</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

### INDEX TEST

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Index test</strong></th>
<th>All entries into the primary care records for 2 years before diagnosis were coded, blinded to case/control status, using the International Classification of Primary Care-2. Only variables occurring in &gt;2.5% of cases or controls were analysed.</th>
</tr>
</thead>
</table>

Are the index test results interpreted without knowledge of the results of the reference standard?  
Yes

*For diagnostic case-control studies:*  
Investigators were kept 'blind' to other important confounding and prognostic factors?  
Yes

**Could the conduct or interpretation of the index test have introduced bias?**  
Low risk

### Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?**  
Low concern

### REFERENCE STANDARD

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Reference standard(s)</strong></th>
<th>Prostate cancer code, from 1998 to 2002 inclusive, in the cancer registry at the Royal Devon and Exeter Hospital or the general practice records</th>
</tr>
</thead>
</table>

Is the reference standard likely to correctly classify the target condition?  
Yes

Were the reference standard results interpreted without knowledge of the results of the index tests?  
Unclear

**Could the reference standard, its conduct, or its interpretation have introduced bias?**  
Low risk

### Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?**  
Low concern

### FLOW AND TIMING

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Flow and timing</strong></th>
<th>All patients appears to be accounted for</th>
</tr>
</thead>
</table>

Was there an appropriate interval between index test and reference standard?  
Yes

Did all patients receive the same reference standard?  
Yes

Were all patients included in the analysis?  
Yes

**Could the patient flow have introduced bias?**  
Low risk

### NOTES

**Hippisley-Cox (2011)**

### PATIENT SELECTION

<table>
<thead>
<tr>
<th><strong>A. Risk of bias</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Patient sampling</strong></th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
</table>
### A. Risk of bias

**Index test**

‘Red-flag’ symptoms: Incident dysphagia, haematemesis, loss of appetite, weight loss, anaemia, and abdominal pain.

Were the index test results interpreted without knowledge of the results of the reference standard?  
Yes

Could the conduct or interpretation of the index test have introduced bias?  
Low risk

### B. Concerns regarding applicability

Are there concerns that the index test, its conduct, or interpretation differ from the review question?  
Low concern

### Reference standard

### Patient characteristics and setting

A total of 1238971 patients were identified from 189 practices (621478 males, 617493 females), mean (SD) age = 50.1 (15) years, mean (SD) Townsend score = -0.2 (3.6).

**Symptoms:**

Current dysphagia (N = 8165), current haematemesis (N = 7119), current abdominal pain (N = 126161), current appetite loss (N = 6133), current weight loss (N = 5377), tiredness in the last year (N = 14119), haemoglobin recorded in the last year (N = 12638, haemoglobin < 11 g/dl in the last year (N = 218862).

**Incident cases of gastro-oesophageal cancer during the 2-year follow up period:**

N = 1343 (776 oesophageal and 567 gastric).

**Inclusion criteria:**

All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

**Exclusion criteria:**

- Patients without a postcode-related Townsend score,
- Patients with a history of gastro-oesophageal cancer at baseline, and
- Patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

**Clinical setting:** Primary care, UK

Are there concerns that the included patients and setting do not match the review question?  
Low concern
### A. risk of bias

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>2-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

### B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

### FLOW AND TIMING

#### A. risk of bias

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>A total of 1342329 patients were initially identified of whom 103358 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of gastro-oesophageal cancer (N = 538), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1238971 patients. However, data is presented for 963040/1238971 patients for all symptoms. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

#### NOTES

Results not presented separately for gastric and oesophageal cancer

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

| Patient characteristics and setting | A total of 1236601 patients were identified from 189 practices (620240 males, 616361 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6). Symptoms: Current rectal bleeding (N = 29118), current abdominal pain (N = 125816), current appetite loss (N = 5358), current weight loss (N = 14065), recent change in bowel habit (N = 1821). Incident cases of colorectal cancer during the 2-year follow up period; |

Hippisley-Cox (2012)
N = 2603 (1562 colon and 1041 rectum).

Inclusion criteria:
All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000); 12 months after the patient registered with the practice; and for those patients with red flag symptoms (see below), the date of the first recorded onset within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of colorectal cancer at baseline, and patients with a recorded ‘red-flag’ symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care, UK

| Are there concerns that the included patients and setting do not match the review question? | Low concern |
|INDEX TEST| |
|A. Risk of bias| |
|Index test| ‘Red-flag’ symptoms: First onset rectal bleeding, first onset loss of appetite, first onset weight loss, first onset abdominal pain, first onset change in bowel habit (in the past 12 months), and anaemia (recorded haemoglobin < 11 g/dl in the past 12 months). |
|Were the index test results interpreted without knowledge of the results of the reference standard? | Yes |
|Could the conduct or interpretation of the index test have introduced bias? | Low risk |
|B. Concerns regarding applicability| |
|Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern |
|REFERENCE STANDARD| |
|A. Risk of bias| |
|Reference standard(s) | 2-year follow up |
|Is the reference standard likely to correctly classify the target condition? | Yes |
|Were the reference standard results interpreted without knowledge of the results of the index tests? | Unclear |
|Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk |
|B. Concerns regarding applicability| |
|Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern |

FLOW AND TIMING
A. Risk of bias
A total of 1342329 patients were initially identified of whom 105728 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of colorectal cancer (N = 2908), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 31973), leaving 1236601 patients. However, data is presented for 1235547/1236601 patients for all symptoms apart from change in bowel habit, which is only presented for 619651/620240 of the male patients. The missing data does not appear to include any of the cancer cases (although this cannot be ascertained for change in bowel habit), but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.

**Was there an appropriate interval between index test and reference standard?**  Yes

**Did all patients receive the same reference standard?**  Yes

**Were all patients included in the analysis?**  No

**Could the patient flow have introduced bias?**  Low risk

**NOTES**

Please note there is some overlap between this patient sample and that of Parker (2007)

**Hippisley-Cox (2012a)**

**PATIENT SELECTION**

**A. risk of bias**

**Patient sampling**

Prospective patient series using patients in the QResearch database (version 30).

**Was a consecutive or random sample of patients enrolled?**  Yes

**Was a case-control design avoided?**  Yes

**Did the study avoid inappropriate exclusions?**  Yes

**Could the selection of patients have introduced bias?**  Low risk

**B. Concerns regarding applicability**

**Patient characteristics and setting**

A total of 1243740 patients were identified from 189 practices (624352 males, 619388 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).

Current symptoms and symptoms in the preceding year:

- Current dysphagia (N = 8507), current abdominal pain (N = 129924), current abdominal distension (N = 4929), current appetite loss (N = 5567), current weight loss (N = 14686), constipation in the last year (N = 8476), diarrhoea in the last year (N = 12233), tiredness in the last year (N = 12688), itching in the last year (N = 1454), haemoglobin recoded in the last year (N = 214497), haemoglobin < 11 g/dl in the last year (N = 16172).

Incident cases of pancreatic cancer during the 2-year follow up period:  N = 781.

**Inclusion criteria:**

All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1
January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information pertaining to these patients will be reported.

Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of pancreatic cancer at baseline, and patients with a recorded ‘red-flag’ (see “Definition of symptom” below) symptom in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDEX TEST</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Index test</td>
<td>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of pancreatic cancer; that is, symptoms of dysphagia, loss of appetite, weight loss, abdominal distension or abdominal pain.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the conduct or interpretation of the index test have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>REFERENCE STANDARD</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Pancreatic cancer, which was defined as incident diagnosis of pancreatic cancer during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 code (157) or ICD-10 diagnostic codes (C25).</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td>Could the reference standard, its conduct, or its interpretation have introduced bias?</td>
<td>Low risk</td>
</tr>
<tr>
<td>B. Concerns regarding applicability</td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>FLOW AND TIMING</td>
<td></td>
</tr>
<tr>
<td>A. Risk of bias</td>
<td></td>
</tr>
<tr>
<td>Flow and timing</td>
<td>A total of 1342329 patients were initially identified of whom 98589 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of pancreatic cancer (N = 96), and ≥ one ‘red flag’ symptom</td>
</tr>
</tbody>
</table>
recorded in the 12 months prior to study entry (N = 27646), leaving 1243740 patients. However, data is presented for 971706 / 1243740 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic cases, i.e., false positives.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

### NOTES

Hippisley-Cox (2012b)

### PATIENT SELECTION

#### A. risk of bias

<table>
<thead>
<tr>
<th>Patient sampling</th>
<th>Prospective patient series using patients in the QResearch database (version 30).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>Low risk</td>
</tr>
</tbody>
</table>

#### B. Concerns regarding applicability

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>A total of 1240722 patients were identified from 189 practices (622166 males, 618556 females), mean (SD) age = 50.1 (14.9) years, mean (SD) Townsend score = -0.2 (3.6).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current symptoms and symptoms in the preceding year:</td>
<td>Current haematuria (N = 25553), current abdominal pain (N = 128721), current appetite loss (N = 5531), current weight loss (N = 14464), constipation in the last year (N = 8472), diarrhoea in the last year (N = 12171), tiredness in the last year (N = 12669), haemoglobin recoded in the last year (N = 216201), haemoglobin &lt; 11 g/dl in the last year (N = 16169).</td>
</tr>
<tr>
<td>Incident cases of renal tract cancer during the 2-year follow up period:</td>
<td>N = 1622; mean age at diagnosis = 70 years, 1187 males/ 435 females; Type of cancer: Bladder: N = 1292; Kidney: N = 307; Ureter: N = 21; Urethra: N = 2.</td>
</tr>
</tbody>
</table>
| Inclusion criteria:                                                           | All practices in England and Wales that had been using their Egton Medical Information Systems (EMIS) computer system for ≥ a year were included. Two-thirds of practices were randomly allocated to the derivation dataset and the remaining practices were allocated to the validation dataset. An open cohort of patients aged 30–84 years was identified, drawn from patients registered with practices between 1 January 2000 and 30 September 2010. Entry to the cohort was defined as the latest of the study start date (1 January 2000) and 12 months after the patient registered with the practice, ensuring that all patients had ≥ 12 months’ registration prior to study entry. For patients with incident haematuria, appetite loss, weight loss, or abdominal pain, the entry date was the date of the first consultation with the symptom within the study period. The relevant data for the present purposes is only available for the validation cohort, therefore only information.
Exclusion criteria: Patients without a postcode-related Townsend score, patients with a history of renal tract cancer at baseline, and patients with a recorded ‘red-flag’ symptom (see “Definition of symptom” below) in the 12 months prior to the study entry date.

Clinical setting: Primary care

<table>
<thead>
<tr>
<th>Are there concerns that the included patients and setting do not match the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**INDEX TEST**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Index test</th>
<th>‘Red-flag’ symptoms were defined as symptoms that might alarm the patient and also indicate the presence of renal tract cancer; that is, symptoms of haematuria, loss of appetite, weight loss, or abdominal pain.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the conduct or interpretation of the index test have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**REFERENCE STANDARD**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Reference standard(s)</th>
<th>Renal tract cancer, which was defined as incident diagnosis of cancer of the bladder, kidney, ureter, or urethra during the 2 years after study entry, recorded either on the patient’s GP record using the relevant UK diagnostic Read Codes, or their linked Office for National Statistics cause-of-death record, using the relevant ICD-9 codes (188 or 189) or ICD-10 diagnostic codes (C64–67).</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Could the reference standard, its conduct, or its interpretation have introduced bias?</th>
<th>Low risk</th>
</tr>
</thead>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Are there concerns that the target condition as defined by the reference standard does not match the question?</th>
<th>Low concern</th>
</tr>
</thead>
</table>

**FLOW AND TIMING**

**A. Risk of bias**

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th>A total of 1342329 patients were initially identified of whom 101607 patients were excluded for the following reasons: No recorded Townsend score (N = 70847), history of renal tract cancer (N = 1506), and ≥ one ‘red flag’ symptom recorded in the 12 months prior to study entry (N = 29254), leaving 1240722 patients. However, data is presented for 967681 / 1240722 patients. The missing data does not appear to include any of the cancer cases, but it is unclear whether some of the missing data includes symptomatic patients, i.e., false positives.</th>
</tr>
</thead>
</table>

<p>| Was there an appropriate interval between index test and reference standard? | Yes |</p>
<table>
<thead>
<tr>
<th><strong>PATIENT SELECTION</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Patient sampling</td>
<td>Case-control study using The Health Improvement Network (THIN) database, which had data from 446 UK general practices with a total of 8.2 million patients.</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No (for derivation cohort) Yes (for validation cohort)</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td></td>
</tr>
<tr>
<td>Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies:</td>
<td></td>
</tr>
<tr>
<td>The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk (for derivation cohort) Low risk (for validation cohort)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>B. Concerns regarding applicability</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics and setting</strong></td>
<td></td>
</tr>
<tr>
<td>Validation cohort:</td>
<td>N = 1826293 (886994 males/939299 females). Age: Not reported. Incident cases of lung cancer during the 1-year follow up: N = 1728.</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>Cases:</td>
<td>All incident cases of lung cancer diagnosed between 1 January 2000 and 28 July 2009 in patients aged ≥ 40 years.</td>
</tr>
<tr>
<td>Controls:</td>
<td>Ten randomly selected controls aged ≥ 40 years with ≥ 1 year of active records were matched to each case on general practice. Validation cohort: All THIN patients aged &gt; 39 years, free from lung cancer on 29 July 2009, and ≥ 1 year general practice follow up.</td>
</tr>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td></td>
</tr>
<tr>
<td>Cases:</td>
<td>Patients with &lt; 1 year of active records prior to their first diagnosis of lung cancer.</td>
</tr>
<tr>
<td>Clinical setting: Primary care, UK.</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

**Are there concerns that the included patients and setting do not match the review question?** Low concern

## INDEX TEST

### A. Risk of bias

**Index test**

Cough, chest/shoulder pain, dyspnoea, weight loss, hoarseness, upper and lower respiratory tract infections, non-specific chest infections, constipation, depressive disorders, and chronic obstructive pulmonary disease (COPD), recorded over the 2-year period before lung cancer diagnosis.

<table>
<thead>
<tr>
<th>Were the index test results interpreted without knowledge of the results of the reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

*For diagnostic case-control studies:*

Investigators were kept 'blind' to other important confounding and prognostic factors?

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

**Could the conduct or interpretation of the index test have introduced bias?**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

## B. Concerns regarding applicability

**Are there concerns that the index test, its conduct, or interpretation differ from the review question?** Low concern

## REFERENCE STANDARD

### A. Risk of bias

**Reference standard(s)** Lung cancer diagnosis in THIN database

<table>
<thead>
<tr>
<th>Is the reference standard likely to correctly classify the target condition?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were the reference standard results interpreted without knowledge of the results of the index tests?</th>
<th>Unclear</th>
</tr>
</thead>
</table>

**Could the reference standard, its conduct, or its interpretation have introduced bias?**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

## B. Concerns regarding applicability

**Are there concerns that the target condition as defined by the reference standard does not match the question?** Low concern

## FLOW AND TIMING

### A. Risk of bias

<table>
<thead>
<tr>
<th>Flow and timing All the patients are accounted for.</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was there an appropriate interval between index test and reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did all patients receive the same reference standard?</th>
<th>Yes</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Were all patients included in the analysis?</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Could the patient flow have introduced bias?**

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
</table>

## NOTES

Panzuto (2003)

## PATIENT SELECTION

### A. Risk of bias

**Patient sampling**

Prospective 8-week study of patients presenting to 159 primary care physicians (approximately 63600 patient visits during the study period)
Was a consecutive or random sample of patients enrolled? | No  
---|---
Was a case-control design avoided? | Yes  
Did the study avoid inappropriate exclusions? | Unclear  
Could the selection of patients have introduced bias? | High risk  

B. Concerns regarding applicability

| Patient characteristics and setting | N = 280; 120 males, 160 females; median age (range) = 61 (18-87) years.  
---|---
Inclusion criteria: Consecutive patients who consulted their GP “with symptoms considered suspicious for the presence of a colon disease to rule out the presence of colorectal cancer” and who were investigated with a colonoscopy or double-contrast barium enema [The decision of how (colonoscopy or double-contrast barium enema) and when to investigate the colon was made only by the physicians on the basis of the clinical evaluation during the visit].  
Exclusion criteria: Patients with previous diagnoses of colorectal disorders or a recent large bowel examination.  
Clinical setting: Primary care, Italy.  

Are there concerns that the included patients and setting do not match the review question? | Unclear concern  

INDEX TEST

A. Risk of bias

| Index test | Abdominal pain, bloating, constipation, rectal bleeding, diarrhoea, iron-deficiency anaemia (haemoglobin levels < 14 g/dl for males and < 12 g/dl for females, in the presence of ferritin < 30 µg/l and a median corpuscular value < 80 fl), change in bowel habits (onset of diarrhoea or constipation or altered stool in the previous 3 months) and weight loss (decrease of ≥ 3 kg in the 3 months prior to the visit).  
---|---
Were the index test results interpreted without knowledge of the results of the reference standard? | Yes  
Could the conduct or interpretation of the index test have introduced bias? | Low risk  

B. Concerns regarding applicability

| Are there concerns that the index test, its conduct, or interpretation differ from the review question? | Low concern  

REFERENCE STANDARD

A. Risk of bias

| Reference standard(s) | Histology  
---|---
Is the reference standard likely to correctly classify the target condition? | Yes  
Were the reference standard results interpreted without knowledge of the results of the index tests? | No  
Could the reference standard, its conduct, or its interpretation have introduced bias? | Low risk  

B. Concerns regarding applicability

| Are there concerns that the target condition as defined by the reference standard does not match the question? | Low concern  

---

Suspected Cancer: Appendix F (June 2015)  
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**FLOW AND TIMING**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow and timing</td>
<td>56/332 patients were excluded due to lack of mandatory fields (age, sex, clinical history, presenting symptoms and procedure results) in the database (N = 35) or violation of exclusion criteria (N = 18)</td>
</tr>
<tr>
<td>Was there an appropriate interval between index test and reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Did all patients receive the same reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all patients included in the analysis?</td>
<td>No</td>
</tr>
<tr>
<td>Could the patient flow have introduced bias?</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

**NOTES**

Stapley (2012)

**PATIENT SELECTION**

<table>
<thead>
<tr>
<th>A. risk of bias</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sampling</td>
<td>Matched case-control study using patients in the UK’s General Practice Research Database (GPRD).</td>
</tr>
<tr>
<td>Was a consecutive or random sample of patients enrolled?</td>
<td>No</td>
</tr>
<tr>
<td>Was a case-control design avoided?</td>
<td>No</td>
</tr>
<tr>
<td>Did the study avoid inappropriate exclusions?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: Attempts were made within the design or analysis to balance the comparison groups for potential confounders?</td>
<td>Yes</td>
</tr>
<tr>
<td>For diagnostic case-control studies: The groups were comparable at baseline, including all major confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td>Could the selection of patients have introduced bias?</td>
<td>High risk</td>
</tr>
</tbody>
</table>

**B. Concerns regarding applicability**

<table>
<thead>
<tr>
<th>Patient characteristics and setting</th>
<th>Cases:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 3635, 1743 males / 1892 females; median number of consultations = 18 (IQR = 11-27); aged 40-49 years: N = 107; 50-59 years: N = 529; 60-69 years: N = 829; 70-79 years: N = 1212; ≥ 80 years: N = 958; UK.</td>
</tr>
<tr>
<td></td>
<td>Controls:</td>
</tr>
<tr>
<td></td>
<td>N = 16459, gender not reported; median number of consultations = 9 (IQR = 4-15); aged 40-49 years: N = 422; 50-59 years: N = 2239; 60-69 years: N = 3755; 70-79 years: N = 5702; ≥ 80 years: N = 4341; UK.</td>
</tr>
<tr>
<td>Inclusion criteria:</td>
<td>Cases: Patients with a record of one of 25 GPRD pancreatic cancer codes between January 2000 and December 2009 inclusive, aged ≥ 40 years, with min. 1 year of data before diagnosis. The first instance of a pancreatic cancer code was assigned the data of diagnosis/index date.</td>
</tr>
<tr>
<td></td>
<td>Controls: Up to 5 controls were matched to cases on sex, general practice, and to 1 year of age of the case. The index date was the index date of the matched case.</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: Pancreatic cancer (controls), no consultations in the year before diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Clinical setting: Primary care</td>
</tr>
<tr>
<td>Are there concerns that the included patients and setting do not match the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>INDEX TEST</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. Risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong></td>
<td>All symptoms, physical signs or abnormal investigations compiled from the pancreatic cancer literature were studied, and supplemented by discussion with two pancreatic cancer charities. Libraries of codes relating to these were collated. All codes for fractures were also identified, as a test for any recording bias between cases and controls (making the assumption that the fracture rate would be approximately equal). Occurrences of these features in the year before the index date were identified. Features were only retained for further study if they occurred in ( \geq 5% ) of cases or controls. Repeat attendances with the same symptom were also retained if the subsequent consultation also occurred in ( \geq 5% ) of cases or controls. New-onset diabetes was defined as a code for diabetes, or a random blood glucose above the local laboratory's normal range, without similar codes more than 1 year before the index date. For laboratory tests, patients without a test were considered to be the same status as those with a normal result, making our binary variable abnormal result/ no abnormal result. Abnormal liver function was defined as any liver enzyme above the normal range, and raised inflammatory markers as either abnormal erythrocyte sedimentation rate or C-reactive protein, as there were too few plasma viscosity results.</td>
</tr>
<tr>
<td>Were the index test results interpreted without knowledge of the results of the reference standard?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>For diagnostic case-control studies:</strong> Investigators were kept 'blind' to other important confounding and prognostic factors?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Could the conduct or interpretation of the index test have introduced bias?</strong></td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
</tr>
<tr>
<td>Are there concerns that the index test, its conduct, or interpretation differ from the review question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>REFERENCE STANDARD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td>Pancreatic cancer code in the UK's General Practice Research Database.</td>
</tr>
<tr>
<td>Is the reference standard likely to correctly classify the target condition?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the reference standard results interpreted without knowledge of the results of the index tests?</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Could the reference standard, its conduct, or its interpretation have introduced bias?</strong></td>
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<tr>
<td><strong>B. Concerns regarding applicability</strong></td>
<td></td>
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<tr>
<td>Are there concerns that the target condition as defined by the reference standard does not match the question?</td>
<td>Low concern</td>
</tr>
<tr>
<td><strong>FLOW AND TIMING</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A. risk of bias</strong></td>
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<tr>
<td>Flow and timing</td>
<td>A total of 21624 patients were identified, 17977 controls and 3647 cases. Of</td>
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</table>
the controls the following exclusions were applied: pancreatic cancer (N = 64), case excluded (N = 40), and no data in year pre-index date (N = 1414). Of the cases the following exclusions were applied: No controls (N = 2), and cancer not of pancreatic origin (N = 10).

Was there an appropriate interval between index test and reference standard? Yes

Did all patients receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the patient flow have introduced bias? Low risk

NOTES

References

Included studies
