

2019 surveillance of suspected cancer: recognition and referral (NICE guideline NG12)

Surveillance proposal

We will not update the guideline on [suspected cancer: recognition and referral](#).

Reasons for the proposal

New evidence and information identified during was considered not to have an impact on current guideline recommendations.

Symptoms of suspected cancer

Topic experts had varied views regarding the need for updating the guideline. Half of the topic experts consulted noted that the guideline needs to be updated. They highlighted new evidence supporting current guideline recommendations. Some topic experts noted new symptoms that could be added into some cancers (such as cervical or breast cancer), some areas of interest such as the use of faecal immunological tests (FIT) or new relevant areas of interest (such as artificial intelligence or the use of electronic health records). Information gathered during this surveillance review highlighted similar areas to those noted by topic experts, including the use of FIT in colorectal cancer, new symptoms in some types of cancers (such as throat pain in oral cancer), or new cancers (such as hypopharyngeal or pharyngeal cancer). Overall, we did not identify new evidence to support the inclusion of new symptoms, cancers or tests; or the evidence identified was considered limited in terms of the quantity and quality (number and type of observational studies, small sample sizes or relevant outcomes reported in the abstract) to warrant an update of the recommendations.

Non-site-specific symptoms

One of the topic experts highlighted that new evidence was available on weight loss and suspected cancer. We identified new evidence that supports current guideline recommendations on assessing people with unexplained weight loss because it is a symptom of several cancers.

Patient information and support

New evidence identified showed the relevance of considering patient preferences in the diagnostic process for prostate cancer in primary care, as well as engaging with patients considering any relevant factors such as health beliefs and concerns. This new evidence was considered to support current guideline recommendations in this section which state discussing with patients their preferences and involve them in the decision-making process about referral options and further investigations including the potential benefits and harms of the interventions. It also links to the patient experience in adult NHS services guideline which provide additional guidance in this area, helping people engage with healthcare services.

The diagnostic process

We identified new evidence on several aspects of the diagnostic process including: assessing the impact of the urgent referral pathway in primary care; evaluating the impact of undertaking additional primary care investigations in patients who do not fulfil the criteria for urgent referral, and the use of electronic health records and decision support tools. New evidence identified supports the use of the two-week referral pathway for suspected cancer. NICE guideline NG12 recommends that arrangements need to be in place to support non-urgent referrals and any additional investigations, to reduce the impact on the time to be referred to secondary care. The use of electronic health records and decision support tools is an emerging area of interest, but more research is needed to assess the effectiveness of those interventions in referral for suspected cancer.

Primary care testing

We identified new evidence on primary care testing, around the role of inflammatory markers for cancer diagnosis in primary care, or the use of urinary biomarkers (Cxbt) in patients with haematuria. However, the evidence was considered limited in terms of the study design, the number of patients included and conclusions to have an impact on current guideline recommendations.

For further details and a summary of all evidence identified in surveillance, see the [summary of evidence from surveillance](#).

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in [suspected cancer: recognition and referral](#) (NICE guideline NG12) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update proposals that are available, see [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 63 studies in a search for primary care-based studies published between January 2014 and August 2019. Topic experts identified 14 studies, 12 were considered relevant. All of them were also identified in the literature searches, so no new studies were added.

See the [summary of evidence from surveillance](#) for details of all evidence considered, and references.

Selecting relevant studies

We included only primary care-based studies, as people with symptoms in primary care were the population of relevance to this guideline. We included relevant references that described important information about cancer symptoms in their abstracts such as positive predictive values (PPVs), sensitivities, specificities, likelihood ratios (LRs), or odds ratios (ORs). We also included primary care-based studies on investigations for cancer in primary care following the same inclusion criteria used for cancer symptoms.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 6 were assessed as having the potential to change recommendations.

Therefore, we plan to regularly check whether these studies have published results and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- [Raman spectroscopy and colorectal cancer](#)
 - This is randomised controlled trial assessing the diagnostic accuracy of the Raman spectroscopy test which is a blood test that can be used in primary care in symptomatic patients to achieve an earlier diagnosis of bowel cancer.
- [FIT— Can a Dipstick Test Rule Out Bowel Cancer?](#)

- This is a non-randomised diagnostic study assessing the accuracy of FIT to triage symptomatic patients for a suspected cancer referral for bowel cancer in primary care.
- [Biomarkers for ovarian cancer risk assessment](#)
 - This is a case series pilot study assessing the accuracy of the HE and CA125 biomarkers in risk assessment of symptomatic patients in primary care.
- [CANcer Diagnosis Decision rules](#)
 - This is an observational cohort study aiming to identify alarm symptoms and signs for early prediction of lung and colon cancer.
- [Detection of bowel cancer using urinary biomarkers](#)
 - This is a feasibility study evaluating the diagnostic accuracy of urinary biomarkers for the detection of colorectal cancer and polyps in symptomatic patients.
- [Electronic Risk Assessment for Cancer for Patients in General Practice](#)
 - This is pragmatic cluster randomised controlled trial investigating the effectiveness of electronic risk assessment tools for lung, colorectal oesophago-gastric, bladder, kidney, and ovarian cancer in primary care.

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 14 topic experts and received 8 responses. The topic experts who provided feedback were: GPs, public health consultant, clinical reader, consultant radiologist, and a consultant oncologist. We also received feedback from Macmillan Cancer Support and their GP Advisers (one questionnaire received).

Overall, 4 topic experts thought that the guideline should be updated and 4 thought that an update was not necessary. The issues that topic experts thought could be addressed in an update were:

- Colorectal cancer. The use of FIT in symptomatic patients in primary care was highlighted as an area of interest in colorectal cancer. Also, the need to reinstate the symptoms profile of low-risk patients into the recommendations. The symptoms profile of low-risk patients was removed following the introduction of NICE guidance on [quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care \(DG30\)](#) in this area. We identified evidence supporting the use of FIT to rule out cancer in symptomatic patients. Regarding the symptoms profile of low-risk patients, we will pass this information onto the diagnostics guidance team so it could be considered in the next review of NICE guidance DG30.
- Alarm symptoms in suspected cancer. Topic experts noted that there was new evidence on alarm symptoms in different types of cancer including cervical cancer, testicular cancer, laryngeal cancer, brain cancer, leukaemia, non-Hodgkin's lymphoma, and Hodgkin's lymphoma. They also mentioned symptoms that need to be removed such a neck lump in laryngeal cancer or symptoms that should be considered, such as persistent areas of asymmetrical modularity or persistent skin changes in breast cancer. We identified new evidence in those cancers, and other cancers considered in the guideline including lung cancer, upper and lower gastrointestinal tract cancers, other gynaecological and urological cancers, skin cancers, and other head and neck cancers. In general, the evidence identified came from observational studies (or systematic reviews of observational studies) and reported different outcomes (PPVs, LRs, ORs or frequencies). Most of the symptoms (and combinations of symptoms) described in the studies were included in current guideline recommendations. In other cases, no new evidence was identified in the symptoms highlighted by the topic experts or some new symptoms were identified but the evidence found was considered limited to warrant an update of the recommendations (a small number of studies identified, no

relevant outcomes described in the abstract, small sample sizes, among others). See the [NICE guideline NG12 evidence summary](#) for further details on the evidence identified for each cancer.

- Ovarian cancer. One of the topic experts highlighted that the measurement of serum CA125 as a first diagnostic test of ovarian cancer in primary care needs to be reassessed, given the growing doubt among clinicians about its utility in this context. It was also highlighted that the current approach of limiting the access to ultrasound scans only to those women with raised CA125 might have an impact on diagnosis and miss early tumours. We did not identify relevant evidence in this area. This particular topic was considered in 2 previous [surveillance reviews](#) of the NICE guideline on ovarian cancer (the last one published in 2017) and the evidence identified in those surveillance reviews was considered unlikely to change guideline recommendations.
- Electronic health records for risk assessment of cancer in primary care. This area was raised by topic experts as an ongoing research area relevant to this guideline. New relevant evidence considered during this surveillance review suggests that information technology tools could be useful to identify patients with cancer, but more research is needed to assess the effectiveness of those interventions in suspected cancer in primary care.
- Rapid diagnostic centres. One topic expert noted the emergence of rapid diagnostic centres and the need for recommendations in this area. We did not identify new evidence on rapid diagnostic centres. This area is not currently covered in the guideline, and no new evidence was identified through the surveillance review to indicate that this section should be added.
- Other areas of interest were diagnostic tests in primary care, use of artificial intelligence and shared decision-making (please see further details in the [NICE guideline NG12 evidence summary document](#)). We did not identify any evidence to suggest these areas should be updated.

Views of stakeholders

Stakeholders are consulted on all surveillance reviews except if the whole guideline will be updated and replaced. Because this surveillance proposal is to not update the guideline, we are consulting with stakeholders.

See [ensuring that published guidelines are current and accurate](#) in developing NICE guidelines: the manual for more details on our consultation processes.

Implementation of the guideline

A total of 6 experts provided information on the implementation of the guideline. Overall, it was considered that the guideline is well implemented. Also, resources such as [The cancer maps](#) developed by Dr Ben Noble, which summarise the NICE guideline NG12 recommendations were highlighted as very valuable for the implementation of the guideline in primary care.

Equalities

No equalities issues were identified during the surveillance process.

Overall proposal

After considering all evidence and other intelligence and the impact on current recommendations, we decided that no update is necessary.

Appendix A: Summary of evidence from surveillance

2019 surveillance of suspected cancer: recognition and referral (2015) NICE guideline NG12

Summary of evidence from surveillance

Studies identified in this surveillance review are summarised from the information presented in the abstract of the studies.

Only primary care based studies were included. The positive predictive values (PPVs) are described if they were included in the abstract of the studies.

Other outcomes such as sensitivities, specificities, likelihood ratios (LR), odds ratios (OR) or frequency of the symptoms are also described if reported.

If a systematic review (SR) was identified in a specific area, only the primary studies published in the same year or the year after the publication of the SR were summarised, due to the volume of evidence identified.

The use of the information only described in the abstracts is limited in that it is likely that only symptoms with high PPVs are described in the abstract, so it was not possible to assess any other symptoms not reported in the abstract but included in the full text of the study.

To reach a view on the need to update each section of the guideline, we considered feedback from topic experts who advised us on the approach to this surveillance review alongside the evidence identified. We also considered all other correspondence received since the guideline was published.

1.1 Lung and pleural cancers

[Lung cancer](#)

Surveillance proposal

The section of the guideline on [lung cancer](#) should not be updated.

2019 surveillance summary

Symptoms

A systematic review (SR) assessed the symptoms related to lung cancer [Okoli G. et al. 2018]. A total of 13 diagnostic studies using primary and secondary care data were included. Diagnostic ORs and summary receiver operating characteristic curves were calculated. Haemoptysis, dyspnoea, cough and chest pain were identified as the symptoms with higher diagnostic value for lung cancer. All these symptoms had an area under the curve (AUC) over 0.6 and were considered to have good discriminatory power. We identified an observational study published assessing symptom lead time distribution in lung cancer [Ades AE et al. 2014]. Given that this study was published before the SR, the results of this study are not summarised in this surveillance report.

A SR assessed the positive predictive value (PPV) of alarm symptoms for colorectal, breast, prostate and lung cancer in primary care [Huggenberger IK et al. 2015]. A total of 16 studies were included (unclear from the abstract if only primary care data were used). The PPV for haemoptysis varied from 8.4 (people aged 55 years) to 20.4 (people above 85 years). The PPVs for cough, thorax pain, and general symptoms varied from 0.4% to 1.1%. Authors suggested that a model combining different symptoms and risk factors may improve the diagnosis of the cancers assessed in primary care.

One observational study assessed the predictive value of symptoms for different cancers [van Boven K et al. 2017]. It was a retrospective analysis of a cohort of patients over 45 years in primary care in the Netherlands (118,219 patient-years analysed). The study focused on alarm symptoms defined by the Dutch Cancer Society and Cancer Research UK. Only symptoms spontaneously mentioned by patients in the clinical appointment were included. The PPV for diagnosing cancer in patients referring haemoptysis was 2.7%. The type of cancer linked to this symptom was not specified in the abstract. Haemoptysis is a symptom included in this section of NICE guideline NG12.

A case-control study conducted in Sweden assessed the clinical features of patients with cancer frequently attending primary care before diagnosis [Ewing M et al. 2018]. The cancers studied were prostate, breast, colorectal, lung, gynaecological, and skin cancer. The study included a total of 2,759 patients with cancer who attended their GP practice 4 times or more 1-year before

diagnosis. The cases were matched with 9,424 controls. Data on diagnosis codes and related health problems were extracted from a national cancer register and regional databases. Sixty percent of the codes with the highest likelihood ratios (LR) were alarm symptoms or signs of the cancers studied. The symptom with the highest LR for cancer was breast lump. No specific symptoms associated with lung cancer were described in the abstract. Abnormal levels of plasma proteins and serum enzyme levels were also associated with cancer (the specific cancer was not described in the abstract).

Risk prediction tools in symptomatic patients in primary care

A SR assessed cancer risk predictions tools that could be used in primary care in symptomatic patients that may have lung cancer [Schmidt-Hansen M et al. 2017]. A total of 7 studies were included, all of them evaluating risk prediction tools based on UK primary care data. The tools varied in terms of methods used for their development, criteria included, and time frames to measure important outcomes. Four of them reported AUC values, which ranged from 0.88 to 0.92. Limitations highlighted by the authors included lack of external validation, or clinical and cost impact assessment of the tools assessed. They concluded that the evidence is limited to recommend the use of any of the tools identified.

Thrombocytosis

A SR assessed the role of a raised platelet count in predicting cancer in adults (40 years and over) in primary care [Bailey SER et al. 2017]. A total of 9 observational studies were identified, all of them case-control studies. They assessed the predictive value of thrombocytosis in different cancers including colorectal, lung, ovarian, bladder, renal, pancreatic, esophagogastric, uterus and breast cancer. The analysis showed that thrombocytosis could be an early marker of lung cancer, but no specific data were provided in the abstract. Authors concluded that more research is needed to study the association between thrombocytosis and cancer. An observational study published in the same year assessed the incidence of cancer in patients with thrombocytosis in primary care settings [Bailey SEr et al. 2017]. The study analysed data of 39,230 patients extracted from the Clinical Practice

Research Datalink database in the UK. A total of 31,249 patients had thrombocytosis. Approximately 8% of them (2453) were diagnosed with cancer, 44% (1098) were males. The risk of cancer increased when a second test reporting thrombocytosis was recorded within 6 months. The most common cancers diagnosed were lung and colorectal cancer, with thrombocytosis being the only feature presented in one third of the patients.

Low-dose computed tomography scan

A study assessed the use of low-dose computed tomography (CT) scan in the diagnosis of lung cancer in primary care settings (Denmark). [Guldbrandt LM et al. 2015; Guldbrandt LM et al. 2015]. A total of 119 general practices were randomised to direct access to low-dose CT scan in patients with a suspicion of lung cancer who did not meet the referral criteria to secondary care (fast-track referral) or standard care. A total of 331 patients were included. No differences were identified in terms of diagnosis stage and time to diagnosis. Adjusted results by compliance indicated that a direct access to low-dose CT scan seems to decrease the time to diagnosis compared with standard care. Authors concluded that direct access to low-dose CT scan does not have an impact on the diagnosis of lung cancer in symptomatic patients, but a case finding with direct access to low-dose CT could be an alternative to lung cancer screening.

Patients' experiences

A qualitative study explored patients' beliefs and experiences after consulting for cancer-related symptoms in primary care in the UK [Birt L et al. 2014]. A total of 35 adult patients were interviewed after being referred to secondary care (but before being seen by the specialist team). Most of the patients experienced similar symptoms, and their seriousness was contextualised in terms of previous health experiences and comorbidities. Patients sought help if the symptoms did not improve as expected or there was an increased awareness of lung cancer symptoms or if the symptoms presented raised public concern (for example, coughing). Patients highlighted that more guidance is needed for them in terms of how to monitor symptoms and when to reconsult to primary care.

Intelligence gathering

Topic experts consulted during this surveillance review mentioned the use of low-dose CT as a diagnostic modality, as well as the increased availability of MRI/CT scans in health services.

Impact statement

In the original guideline, the guideline committee noted that haemoptysis was the only single symptom with a PPV >3%. They considered, based on their experience, other symptoms with PPVs below the 3% threshold that were indicative of lung cancer. Smoking history was also highlighted as a relevant factor to consider in this context. Evidence identified in this surveillance review indicated that the PPV for haemoptysis is close to or above 3% in line with current guideline recommendations. Evidence related to other symptoms, including cough and thorax pain showed variable results with PPVs that ranged from 0.45 to 11%. Cough and chest pain are symptoms included in the recommendations. The PPVs identified in the original guideline were also variable but the guideline committee considered that they were sufficiently indicative of lung cancer. The findings are considered unlikely to change current guideline recommendations.

In the original guideline, it was also noted there was a lack of evidence on the diagnostic accuracy of investigations in primary care settings. The guideline committee considered, based on their experience, that a raised platelet count was likely to be linked to lung cancer. X-rays were also considered to be a relevant test in this context. We identified evidence through this surveillance review on thrombocytosis and lung cancer. However, no data on the PPV were reported in the abstracts of the studies limiting their applicability to the current surveillance review.

Topic experts mentioned that low-dose CT scans as a diagnosis modality for lung cancer in primary care settings is an area of interest. We identified new evidence on cancer risk predictions tools and low-dose CT scan access in primary care. Evidence from one study identified in this area suggests that low-dose CT scans do not have an impact on the diagnosis of lung cancer in symptomatic patients in primary care.

Evidence identified on patient experience support current recommendations on providing patient information and support.

New evidence is unlikely to change guideline recommendations.

Mesothelioma

Surveillance proposal

No new information on [mesothelioma](#) was identified at this surveillance review.

1.2 Upper gastrointestinal tract cancers

Oesophageal cancer

Surveillance proposal

The section of the guideline on [oesophageal cancer](#) should not be updated.

2019 surveillance summary

Symptoms

A SR assessed the presenting symptoms of esophago-gastric cancer in primary care (including open-access endoscopy clinics) [Astin MP et al. 2015]. A total of 14 studies were included. Dyspepsia as a single symptom showed sensitivity and specificity values around 42 to 48% but with wide 95% confidence intervals. Pain and dysphagia as single symptoms also showed low sensitivity values (41% and 32%, respectively) with higher specificity values (75% and 92%, respectively) with wide 95% confidence intervals as well. A similar trend was seen with anaemia, nausea/vomiting/bloating, reflux and weight loss with sensitivity values ranging from 12% to 25% and specificity values ranging from 70% to 97%. Authors concluded that

dysphagia, weight loss, and anaemia are the strongest symptoms linked to oesophageal cancer.

Test in primary care

One study piloted the introduction of an early gastroscopy programme in patients with dyspepsia and alarm signs in primary care (Spain) [Garcia-Alonso FJ et al 2017]. The pilot consisted of direct access to endoscopy from primary care for patients consulting for dyspepsia symptoms and warning signs. A total of 355 patients were included in the 1-year pilot. The early access to gastroscopy had an impact on the reduction of referrals to secondary care.

Intelligence gathering

No relevant information was identified for this section of the guideline

Impact statement

The guideline recommends that symptomatic people are referred to an upper gastrointestinal endoscopy instead of following a suspected cancer pathway referral. The alarm symptoms and combinations included in the recommendations were those with a PPV of 3% or above, and others with a PPV below the 3% were those that the committee considered to be predictive of oesophageal cancer. We identified new evidence supporting the use of similar symptoms in oesophageal cancer. However, we did not identify evidence on the symptom combinations included in the guideline or the influence of other characteristics such as age on the predictive value of those symptoms or combinations recommended for further assessment. We also identified one study on direct referral to upper gastrointestinal endoscopy in symptomatic patients. No important outcomes were reported in the study, but the findings support current guideline recommendations which state offer urgent or non-urgent direct access upper gastrointestinal endoscopy to assess for oesophageal cancer in people depending on the symptoms presented and age.

New evidence is unlikely to change guideline recommendations.

[Pancreatic cancer](#)

Surveillance proposal

The section of the guideline on [pancreatic cancer](#) should not be updated.

2019 surveillance summary

Symptoms

A SR assessed the risk of pancreatic cancer in symptomatic people presenting in primary care [Schmidt-Hansen M et al. 2016]. A total of 8 diagnostic studies were included. The PPV of jaundice in people 40 years was 4.1%, and the predictive value increased with the age of the patients. Authors reported that all the other symptoms assessed had very low PPVs, all below the 3% NICE threshold. Among those, the one with the highest PPV was repeated attendance with abdominal pain (PPV 1%). The review also evaluated symptom combinations. The combinations that included weight loss had the highest PPVs (between 1.5% and 2.7% in people 60 years or older). Authors concluded that jaundice is the only single symptom with a high PPV that needs further investigation for risk of pancreatic cancer. The combination of weight loss with other symptoms was also considered relevant for further investigation.

A study assessed early alarm symptoms in patients with pancreatic ductal adenocarcinoma and biliary tract cancer in primary care in the UK [Keane MG et al. 2014]. Data from 3,621 cases and 15,395 matched controls were assessed using the Health Improvement Network primary care database. Other factors, including the number of visits to the GP before diagnosis or trends in blood tests were also evaluated. They analysed the symptoms presented in the year previous to the diagnosis of cancer. A total of 19 symptoms were associated with both cancers (11 with pancreatic ductal adenocarcinoma, and 8 with biliary tract cancer). Back pain, lethargy and new-onset diabetes were the most relevant alarm symptoms associated with pancreatic ductal adenocarcinoma (odds ratios [ORs] between 1.33 to 2.46).

An observational study assessed the symptoms of presentation in patients with neuroendocrine tumours [Basuroy R et al. 2018]. An on-line survey was responded by 301 patients with gastrointestinal or pancreatic neuroendocrine tumours (setting not specified in the abstract). The most common symptoms of presentation reported were pain, flushing and diarrhoea. The median time to diagnosis was 36 months, with irritable bowel syndrome and dyspepsia the most common incorrect diagnoses made.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

New evidence on jaundice and symptom combinations, including weight loss supports current guideline recommendations. Evidence was also identified on back pain and new-onset diabetes both of which are already recommended in the guideline as alarm symptoms in combination with weight loss. Lethargy and flushing were the only symptoms identified in the surveillance evidence that are not included in the guideline recommendations. However, the evidence identified is from a single observational study that reported only the frequency of the symptoms and not PPVs. So, it is considered that the evidence identified is too limited to warrant an update of the recommendations.

New evidence is unlikely to change guideline recommendations.

[Stomach cancer](#)

Surveillance proposal

No new information on [stomach cancer](#) was identified at this surveillance review.

[Gall bladder cancer](#)

Surveillance proposal

No new information on [gall bladder cancer](#) was identified at this surveillance review

[Liver cancer](#)

Surveillance proposal

The section of the guideline on [liver cancer](#) should not be updated.

2019 surveillance summary

One observational study assessing the time-to-referral for liver cancer reported the most common symptoms of presentation in primary care. [Hughes SL et al. 2016]. Data from 90 patients obtained from the National Audit of Cancer Diagnosis in Primary Care (UK) were analysed. The most common symptoms of presentation were abdominal pain and decompensated liver failure. Twelve per cent of the patients were diagnosed with liver cancer by incidental findings from an abnormal liver function test.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

In the original guideline, the committee considered that upper abdominal pain and jaundice were symptoms that were most likely to be associated with other types of upper gastrointestinal cancers, not liver cancer. So, those symptoms were not included in the liver cancer recommendation. Based on their clinical knowledge, the committee considered that an upper abdominal mass was the symptom with the highest PPV for liver cancer (although likely to be below the 3% threshold). So, they considered that this symptom should prompt further assessment with ultrasound.

New evidence identified in this surveillance review from a single observational study showed that the most common symptoms of presentation of liver cancer

are abdominal pain and decompensated liver failure. However, the study included a small number of patients, and no PPVs were provided in the abstract. Given the limited evidence identified, it is considered that it does not have an impact on the current recommendation.

New evidence is unlikely to change guideline recommendations.

1.3 Lower gastrointestinal tract cancers

Colorectal cancer

Surveillance proposal

The section of the guideline on [colorectal cancer](#) should not be updated.

2019 surveillance summary

Symptoms

A SR assessed the PPVs of alarm symptoms for colorectal, breast, prostate and lung cancer in primary care [Huggenberger IK et al. 2015]. A total of 16 studies were included. The PPV for rectal bleeding varied from 6.6% to 21.2% among the studies included. The PPV increased with age. The PPVs for change in bowel habits and general symptoms as single symptoms ranged from 3.5% to 8.5%. Authors suggested that a model combining different symptoms and risk factors could improve the diagnosis of cancer in primary care (no further details were provided in the abstract).

A total of 7 studies were identified through the surveillance review that published in the same year or after the above SR [Holtedah K et al. 2018, Ewing M et al. 2018, Stapley SA et al. 2017, van Boven K et al. 2017, Ewing M et al. 2016, Van Boxtel-wilms SJM 2016, Hamilton W et al. 2015,] and one before the SR [Chowdhurt ATMD et al. 2014]. Only those published after the SR are summarised below.

A cohort of 6,264 patients from 493 GP practices in 6 different European countries assessed the role of abdominal symptoms in suspected abdominal cancer [Holtedah K et al. 2018]. Over a 10-day period, people consulting with

abdominal pain to the GP practices were included and then followed up 8 months later. Rectal bleeding was the single symptom with the highest adjusted hazard ratio (adjusted by sex and age) of abdominal cancer. Haematuria, rectal bleeding, and involuntary weight loss as single symptoms had PPVs >3%. Authors concluded that abdominal pain is related to any abdominal cancer, and different symptoms could be indicative of colorectal cancer (CRC).

A case-control study conducted in Sweden assessed the clinical features of patients with cancer frequently attending to primary care before diagnosis [Ewing M et al. 2018]. The cancers studied were prostate, breast, colorectal, lung, gynaecological, and skin cancer. The study included a total of 2,759 patients with cancer who attended 4 times or more to the GP 1-year before diagnosis. The cases were matched with 9,424 controls. Data on diagnostic codes and related health problems were extracted from a national cancer register and regional databases. Sixty percent of the codes with the highest likelihood ratios (LR) were alarms symptoms or signs of the cancers studied. The symptom with the highest LR for cancer was breast lump. No specific symptoms associated to CRC were described in the abstract. Abnormal levels of plasma proteins and serum enzyme levels were also associated with cancer (specific cancer not described in the abstract).

A case-control study included more than 11 thousand incident cases of CRC and inflammatory bowel disease (IBD) and analysed the PPVs of different symptoms presented in the year before the diagnosis of these conditions [Stapley SA et al. 2017]. People below 50 years of age were included (1,661 CRC and 9,578 IBD). Data were obtained from the Clinical Practice Research Datalink in the UK. The following combinations of symptoms had PPVs above 3%: 1) rectal bleeding with diarrhoea, thrombocytosis, low mean cell volume, low haemoglobin, or abnormal inflammatory markers; 2) change in bowel habit with low mean cell volume, thrombocytosis, or low haemoglobin; and 3) diarrhoea with thrombocytosis. Authors concluded that abnormal haematological tests combined with rectal bleeding or change in bowel habit are good predictors of CRC/IBD.

One observational study assessed the predictive values of symptoms for different cancers [van Boven K et al. 2017]. It was a retrospective analysis of

a cohort of patients over 45 years in primary care in the Netherlands (118,219 patient-year analysed). The study focused on alarm symptoms defined by the Dutch Cancer Society and Cancer Research UK. Only symptoms spontaneously mentioned by patients in the clinical appointment were included. The PPV for diagnosing cancer in patients presenting rectal bleeding was 2.6% and for changes in bowel habit was 1.8%. The type of cancer linked to these symptoms was not specified in the abstract.

A case-control study of patients selected from the Swedish Cancer Register and a regional healthcare database also assessed the PPV of different symptoms for the diagnosis CRC in primary care [Ewing M et al. 2016]. A total of 542 patients with a diagnosis of CRC (non-metastatic) were included and matched with controls (1:4). PPVs identified for single symptoms were bleeding 3.9% (rectal bleeding, melaena, and gastrointestinal bleeding), anaemia 1.4%, change in bowel habit 1.1%, abdominal pain 0.9%, and weight loss 1.0%. The combinations of symptoms with the highest PPV value were bleeding and change in bowel habit (13.7%); and bleeding plus abdominal pain (12.2%). Authors concluded that bleeding combined with changes in bowel habit, constipation, diarrhoea or abdominal pain are the most important predictors of non-metastatic CRC.

A case-control study assessed the PPVs of different symptoms of presentation of CRC in primary care [van Boxtel-Wilms SJM et al. 2016]. A total of 184 CRC cases and 366 controls matched by age, gender and GP practice were included. The symptoms with positive LR and odds ratios (OR) more likely to predict CRC were: tiredness (significant from 6 months prior to the diagnosis), anaemia (significant 3 months before diagnosis), abdominal pain, rectal bleeding and change in bowel habits/constipation (significant from 6 months before diagnosis), and weight loss (significant 3 months before diagnosis).

A case-control study assessed the clinical features of metastatic breast, colorectal and prostate cancer in primary care in the UK [Hamilton W et al. 2015]. A total of 162 cases who had died with metastatic cancer (breast, CRC, or prostate cancer) were matched with 152 cancer controls without metastasis and 145 healthy controls. The most common symptoms associated with metastatic cancer were vomiting, low back pain, loss of appetite, and shoulder

pain (range of ORs from 1.3 to 5.3). Groin pain and pleural disease were also associated (ORs 10 for both symptoms) but very rare (only 16 cases with groin pain, and 9 with pleural disease).

Thrombocytosis

A SR assessed the role of a raised platelet count in predicting cancer in adults (40 years and over) in primary care [Bailey SER et al. 2017]. A total of 9 observational studies were identified, all of them case-control studies. They assessed the predictive value of thrombocytosis in different cancers including colorectal, lung, ovarian, bladder, renal, pancreatic, esophagogastric, uterus and breast cancer. The analysis showed that thrombocytosis could be an early marker of CRC, but no specific data were provided in the abstract. Authors concluded that more research is needed to study the association between thrombocytosis and cancer. An observational study published in the same year assessed the incidence of cancer in patients with thrombocytosis in primary care settings [Bailey SEr et al. 2017]. The study analysed data of 39,230 patients extracted from the Clinical Practice Research Datalink database in the UK. A total of 31,249 patients had thrombocytosis. Approximately 8% of them (2,453) were diagnosed with cancer, 44% (1,098) were males. The risk of cancer increased when a second test reporting thrombocytosis was recorded within 6 months. The most common cancers diagnosed were lung and CRC, being the only feature presented in one third of the patients.

A similar observational study assessed the cancer incidence in patients with a platelet result at the upper end of the normal range (325-400 x 10⁹/l) [Ankus E et al. 2018]. Data from 2,074 patients obtained from the same database (Clinical Practice Research Datalink) were analysed. The platelet test results were stratified in 3 groups: 325-349 x 10⁹/l; 310-374 x 10⁹/l; and 375-399 x 10⁹/l. Findings showed that the incidence of cancer increased with the platelet count. The most common cancer found was CRC. Authors concluded that a platelet result at the upper level needs to be reviewed alongside other symptoms and reasons for testing. More studies are needed to confirm these results.

Faecal occult blood tests in symptomatic patients

A SR assessed the effectiveness of faecal immunochemical tests (FIT) in symptomatic patients (lower abdominal symptoms) in primary care [Westwood M et al. 2017]. Nine diagnostic studies were included in the review. The results showed sensitivities above 90% for the OC-sensor and MH-JACKarc based on a single faecal sample and a cut-off of 10 µg Hb/g faeces.

Specificities were above 75% for both tests. The accuracy of tests decreased when lower grades of neoplasia were included (for example, including higher risk adenoma). Authors concluded that FIT at a cut-off around 10 µg Hb/g might be adequate to rule out cancer in symptomatic patients.

A prospective study assessed the effectiveness of FIT and faecal calprotectin (FC) test in primary care [Hogberg C et al. 2017]. It also evaluated the added value of a haemoglobin test. A total of 373 consecutive patients that received FIT or FC were included. Patients with a FIT or FC equal or above a cut-off of 100 µg/g were referred to imaging from primary care. Data from iron-deficiency tests, blood counts, as well as symptoms, were collected. FIT and haemoglobin was the most accurate option to predict CRC and IBD (sensitivity of 100% and specificity of 61.7%). Authors concluded that a negative FIT combined with adequate haemoglobin values might be sufficient to rule out CRC and IBD.

Other studies identified in the area

A cohort study of 5,745 patients in the UK diagnosed with colon cancer showed that symptomatic women were more likely than men to receive a diagnosis of a benign condition as the cause of their symptoms prior to their diagnosis of colon cancer [Renzi C et al. 2019]. In women, alarm symptoms such as anaemia, rectal bleeding or change of bowel habit were more likely to be linked to benign conditions, for example, irritable bowel disease or diverticular disease, particularly in those aged 40-59. Authors suggested that a new diagnosis of irritable bowel disease or diverticular disease in these women requires new innovative approaches to rule out colon cancer. A similar study using cancer registry, primary and secondary care data in the UK assessed the impact of comorbidities in the diagnosis of CRC [Renzi C et al 2019]. Findings suggested that comorbidities increased the risk of emergency

presentations of CRC, given that their presence could interfere in the diagnostic processes providing alternative explanatory causes for the symptoms presented. A similar observational study assessed the role of comorbidities in delaying the diagnosis of CRC [Mounce LTA et al. 2017]. Data from 4,512 patients with a diagnostic of CRC included in the Clinical Practice Research Datalink in the UK were analysed. Having a comorbid condition was associated with a delay in the diagnosis of CRC. IBD was the individual condition associated with the longest delay.

Intelligence gathering

Topic experts highlighted the use of FIT for symptomatic patients as an area of interest in CRC. They also mentioned that the symptoms profile of low-risk patients included in the previous version of the guideline is still relevant because it provides necessary details to help the implementation of the NICE guidance DG30 recommendations. Topic experts suggested it would be helpful for users to include the symptoms profile again after it was removed following the introduction of NICE guidance DG30 recommendations in this area. A GP highlighted that patients with Lynch syndrome are not considered in the guideline even if they have an increased risk of CRC.

Impact statement

The guideline recommends a suspected cancer pathway referral for people aged 40 and over and presenting with unexplained weight loss and abdominal pain. The suspected cancer pathway referral is also recommended for people aged 50 and over with unexplained rectal bleeding or for people aged 60 and over with iron-deficiency anaemia or changes in their bowel habit. Those recommendations were based on evidence that showed that these single symptoms or combination of symptoms were associated with a PPV >3%. A referral is also recommended if tests show occult blood in the faeces. Rectal or abdominal mass was also included in the recommendations as well as the combination of rectal bleeding with other unexplained symptoms including abdominal pain, change in bowel habit, weight loss and iron-deficiency anaemia in people aged under 50. We identified new evidence on all the single symptoms included in the recommendations but not in all the

combinations of symptoms included. The majority of the studies identified were observational studies; most of them were case-control studies (one SR of observational studies). They reported different results in the abstract (frequencies of symptoms, PPVs, ORs, positive LRs) and some of them were not specific for CRC (they included other types of cancers). No new single symptoms with a PPV >3% were identified. Regarding symptoms combination, a case-control study suggested that rectal bleeding or change in the bowel habit combined with an abnormal haematological test are good predictors of CRC and IBD. Although this study is not specific for CRC, it is considered that these combinations are broadly included in the guideline recommendations. We identified evidence supporting the combination of rectal bleeding with changes in bowel habit or abdominal pain, both combinations in line with current guideline recommendations.

We also identified evidence through this surveillance review on thrombocytosis and CRC. However, no data on the PPV were reported in the abstracts of the studies limiting their applicability to the current surveillance review.

The guideline also recommends tests for occult blood in faeces in people without rectal bleeding but with unexplained symptoms that do not meet the criteria for referral included in the recommendations described above. This recommendation has been incorporated into NICE guidance NG12 from the NICE guidance DG30 [Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care](#).

We identified one SR and one observational study supporting the use of FIT to rule out cancer in symptomatic patients. The observational studies suggested the association of FIT plus normal haemoglobin levels were sufficient to rule out CRC. Given that it was only one observational study with a small number of patients included it was considered that the evidence identified is limited to warrant an update of this recommendation. Topic experts also highlighted that when this recommendation was updated, the symptoms profile of low-risk patients was removed, and the inclusion of this symptom profile is relevant for better implementation of the guidance. The current standard of care was considered in the NICE diagnostic guideline committee discussions alongside the clinical effectiveness, cost-effectiveness

and other relevant considerations. We will pass this query to the diagnostics guidance team so it could be considered in the next review of NICE guidance DG30.

We identified new evidence from observational studies suggesting that having comorbid conditions may have an impact on the diagnosis of CRC, particularly prolonging the time to diagnosis. The guideline recommends as part of the diagnosis process to take part in continuing education, peer review and other activities to improve and maintain clinical consulting, reasoning and diagnostic skills, so people who may have cancer can be identified at an earlier stage. In the original guideline, the guideline committee considered that there were very few instances where risk factors allowed different recommendations to be made for people with the same symptoms. They actively sought exceptions to this in the evidence searches, but no evidence was found on any risk factor (IBD, previous cancer, multiple polyps, known inherited syndromes – including Lynch syndrome or family history) that affected the PPVs of symptoms for CRC. Similar to the original guideline, we did not identify any new relevant evidence in this area.

New evidence is unlikely to change guideline recommendations.

[Anal cancer](#)

Surveillance proposal

No new information on [anal cancer](#) was identified at this surveillance review.

[1.4 Breast cancer](#)

Surveillance proposal

The section of the guideline on [breast cancer](#) should not be updated.

2019 surveillance summary

A case-control study conducted in Sweden assessed the clinical features of patients with cancer frequently attending to primary care before diagnosis [Ewing M et al. 2018]. The cancers studied were prostate, breast, colorectal, lung, gynaecological, and skin cancer. The study included a total of 2,759 patients with cancer who attended 4 times or more to the GP 1-year before diagnosis. The cases were matched with 9,424 controls. Data on diagnosis codes and related health problems were extracted from a national cancer register and regional databases. Sixty percent of the codes with the highest likelihood ratios (LR) were alarm symptoms or signs of the cancers studied. The symptom with the LR for cancer was breast lump. Abnormal levels of plasma proteins and serum enzyme levels were also associated with cancer (specific cancer not described in the abstract).

One observational study analysed data from the English National Audit of Cancer Diagnosis in Primary Care and assessed the presenting symptom of breast cancer in 2,316 women [Koo MM et al. 2017]. Fifty-six presenting symptoms were identified with the following being the most frequent: breast lump, non-lump breast symptoms such as nipple abnormalities and breast pain, non-breast symptoms such as back pain and weight loss.

One observational study assessed the predictive value of symptoms for different cancers [van Boven K et al. 2017]. The study was a retrospective analysis of a cohort of patients over 45 years in primary care in Netherlands (118,219 patient-years analysed). The study focused on alarm symptoms defined by the Dutch Cancer Society and Cancer Research UK. Only symptoms spontaneously mentioned by patients in the clinical appointment were included. The PPV for diagnosing cancer in patients referring with a breast lump was 14.8%. The type of cancer linked to this symptom was not specified in the abstract.

A SR assessed the PPVs of alarm symptoms for colorectal, breast, prostate and lung cancer in primary care [Huggenberger IK et al. 2015]. A total of 16 studies were included. The PPV for palpable suspected tumour varied from 8.1% to 24% among the studies included. No evidence was identified for the following symptoms: pitting of the skin, papil-areola eczema or ulceration, and

suspected axillary lymph nodes. Authors suggested that a model combining different symptoms and risk factors could improve the diagnosis of cancer in primary care.

A case-control study assessed the clinical features of metastatic breast, colorectal and prostate cancer in primary care in the UK [Hamilton W et al. 2015]. A total of 162 cases who had died with metastatic cancer (breast, colorectal, or prostate cancer) were matched with 152 cancer controls without metastasis and 145 healthy controls. The most common symptoms associated with metastatic cancer were vomiting, low back pain, loss of appetite, and shoulder pain (range of ORs from 1.3 to 5.3). Groin pain and pleural disease were also associated but very rare.

A case-control study using data from the Clinical Practice Research Database in the UK assessed alarm symptoms for breast cancer in women in primary care [Walker S et al. 2014]. The study identified that breast lump, breast pain, nipple retraction and nipple discharge were positively associated to breast cancer. Breast lump had a PPV 4.8% and it increased with age, particularly in women over 70 years.

Intelligence gathering

One of the topic experts suggested it would be useful to include in the guideline other important symptoms associated with breast cancer such as persistent areas of asymmetrical nodularity or mastitis/inflammation which doesn't settle or quickly recurs, or persistent skin changes in the absence of a lump. They also mentioned that the guideline needs to include a section on non-urgent referrals for breast cancer.

Impact statement

The guideline recommends a suspected cancer referral for breast cancer in people aged 30 and over with an unexplained breast lump, or in people aged 50 and over if they have discharge, retraction or other changes of concern in one nipple. A suspected cancer referral pathway is also recommended in people with skin changes that suggest breast cancer or in people aged 30 and over with an unexplained lump in the axilla. The decision to include those symptoms was based on the evidence identified and the clinical knowledge of

the guideline committee. We identified observational studies showing a positive association of most of the symptoms included in the recommendations with breast cancer (no evidence was identified for a lump in the axilla). We identified evidence in other symptoms positively associated with breast cancer but not included in the recommendations such as vomiting, low back pain, loss of appetite or shoulder pain but no PPVs were reported in the abstract, limiting the relevance of the results. Also, these symptoms are not exclusive of breast cancer and could be associated with other cancers/diseases. Most of the evidence identified came from studies not specific for breast cancer and reporting different outcomes. Topic expert suggested the inclusion of other symptoms such as persistent areas of asymmetrical nodularity or mastitis/inflammation which doesn't settle or quickly recurs, or persistent skin changes in the absence of a lump, but we did not identify evidence to support their inclusion in the recommendations. We consider that the evidence identified does not have an impact on current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

[1.5 Gynaecological cancer](#)

[Ovarian cancer](#)

Surveillance proposal

The section of the guideline on [ovarian cancer](#) should not be updated.

2019 surveillance summary

No new evidence was identified in this surveillance review.

Intelligence gathering

One of the topic experts highlighted that the measurement of serum CA125 as a first diagnostic test of ovarian cancer in primary care needs to be reassessed given the growing doubt about its utility in this context. It was also

highlighted that the current approach of limiting the access to ultrasound scans only to those women with raised CA125 might have an impact on diagnosis and miss early tumours.

Impact statement

Topic experts highlighted that the role of the measurement of serum CA125 needs to be reassessed. This particular topic was considered in 2 previous [surveillance reviews](#) of NICE guideline on ovarian cancer (the last one published in 2017) and the evidence identified in those surveillance reviews was considered unlikely to change guideline recommendations. We did not identify any new relevant evidence on CA125.

New evidence is unlikely to change guideline recommendations.

Endometrial cancer

Surveillance proposal

The section of the guideline on [endometrial cancer](#) should not be updated.

2019 surveillance summary

A cohort of 6,264 patients from 493 GP practices in 6 different European countries assessed the role of abdominal symptoms in suspected abdominal cancer [Holtedah K et al. 2018]. Over a 10-day period, people consulting with abdominal pain to the GP practices were included and then followed-up 8 months later. Findings showed that genital bleeding has a high specificity for uterine cancer (no more were data provided in the abstract).

One observational study assessed the predictive value of symptoms for different cancers [van Boven K et al. 2017]. It was retrospective analysis of a cohort of patients over 45 years in primary care in Netherlands (118,219 patient-years analysed). The study focused on alarm symptoms defined by the Dutch Cancer Society and Cancer Research UK. Only symptoms spontaneously mentioned by patients in the clinical appointment were

included. The PPV for diagnosing cancer for postmenopausal bleeding was 3.9%. The type of cancer linked to this symptom was not specified in the abstract.

Intelligence gathering

Topic experts noted that the current NICE guideline NG12 recommendations in this area are different from those included in the more recent guidance issued by the British Society of Gynaecological Cancer (2017). The experts highlighted that the British Society of Gynaecological Cancer recommends a direct ultrasound scan as a first line investigation in symptomatic women. No further investigation is needed unless the symptoms recur. They suggest that the guideline should be updated and offer direct access to ultrasound scan before referring a woman using a suspected cancer pathway referral for endometrial cancer. Only women with recurrent bleeding or a scan showing an endometrial thickness of 4 mm or more should be offered a 2ww referral for endometrial cancer. They considered that this approach would reduce unnecessary referrals, diagnostic tests, and patient anxiety, having also an impact on costs without harming patients.

Impact statement

We identified limited evidence in this area. Two observational studies indicated genital bleeding was an important alarm symptom related to endometrial cancer. One study showed that postmenopausal bleeding has a PPV >3% for cancer. The guideline recommends referring women using a suspected cancer pathway referral for endometrial cancer if they have postmenopausal bleeding, and they are aged 55 and over. Topic experts suggested that direct access ultrasound scans from primary care in symptomatic women instead of offering a suspected cancer pathway referral, will reduce unnecessary secondary care appointments, tests, patient anxiety and costs. They noted that this approach would also align the NICE guideline NG12 recommendations with the guidance provided by the British Society of Gynaecological Cancer. In the original guideline, no evidence for investigations for endometrial cancer was identified. The guideline committee considered that ultrasound scans could have value as an investigation in

primary care to determine if a suspected cancer referral was needed. They considered that the benefits of this test would be to expedite endometrial cancer diagnosis in women whose symptoms may otherwise not be investigated. They considered, based on the evidence, other symptoms different from postmenopausal bleeding, that could fall in this category. They recommend doing an ultrasound scan in those clinical scenarios where an urgent referral was not warranted. New evidence identified in this surveillance review suggests that postmenopausal bleeding has a PPV of 3.7% (above the 3% threshold used in the guideline). So, it supports current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

Cervical cancer

Surveillance proposal

The section of the guideline on [cervical cancer](#) should not be updated.

2019 surveillance summary

An observational study assessed the role of earlier cytology (less than 12 months before diagnosis) in symptomatic young women aged 20-29 years in the UK [Lim AWW et al. 2016]. Data from primary care health records, the national cervical screening database and national audit of cervical cancers were analysed. The prevalence of cervical cancer in this population was between 0.4% to 0.9%. The sensitivity of the test for moderate dyskaryosis was superior to 90% in the different databases assessed, and the PPV ranged between 10% to 30%. In this population, PPV of invasive squamous carcinoma was 25.4% and for severe and worse cytology was 2.0%. Authors considered that cytology could be included as a test to triage symptomatic patients for suspected cancer referral in primary care.

Intelligence gathering

Topic experts highlighted that more guidance is needed around women with unexplained vaginal discharge, post coital bleeding or inter-menstrual bleeding which haven't settled after treatment or after 6-8 weeks. They suggest that these patients should be referred for urgent assessment.

Impact statement

We identified one observational study which assessed the role of cytology in symptomatic women aged 20-29. Although the results of the study suggested it could be used to help the decision of referral in this population, the study has limitations including the use of different databases and registries as sources of data, and the specific population assessed which limit the use of the results. Topic experts suggested new symptoms to be considered in the guideline, but we did not identify new evidence to support any change in the recommendations.

New evidence is unlikely to change guideline recommendations.

Vulval cancer

Surveillance proposal

No new information on [vulval cancer](#) was identified at this surveillance review.

Vaginal cancer

Surveillance proposal

new information on [vaginal cancer](#) was identified at this surveillance review.

[1.6 Urological cancers](#)

[Prostate cancer](#)

Surveillance proposal

The section of the guideline on [prostate cancer](#) should not be updated,

2019 surveillance summary

A SR assessed the PPV of alarm symptoms for colorectal, breast, prostate and lung cancer in primary care [Huggenberger IK et al. 2015]. A total of 16 studies were included. In prostate cancer, the PPV of positive rectal examination was 12% (only one study) and positive value of lower urinary tract symptoms ranged between 1.0% and 3.0%. No evidence was identified for perianal pain and haematospermia. Authors suggested that a model combining different symptoms and risk factors could improve the diagnosis of cancer in primary care.

A case-control study conducted in Sweden assessed the clinical features of patients with cancer frequently attending to primary care before diagnosis [Ewing M et al. 2018]. The cancers studied were prostate, breast, colorectal, lung, gynaecological, and skin cancer. The study included a total of 2,759 patients with cancer who attended 4 times or more to the GP 1-year before diagnosis. The cases were matched with 9,424 controls. Data on diagnosis codes and related health problems were extracted from a national cancer register and regional databases. Sixty percent of the codes with the highest likelihood ratios (LR) were alarms symptoms or signs of the cancers studied. The symptom with the highest LR for cancer was breast lump. No specific symptoms associated to prostate cancer were described in the abstract. Abnormal levels of plasma proteins and serum enzyme levels were also associated with cancer (specific cancer not described in the abstract).

A case-control study assessed the clinical features of metastatic breast, colorectal and prostate cancer in primary care in the UK [Hamilton W et al. 2015]. A total of 162 cases who had died with metastatic disease were matched with 152 cancer controls without metastasis and 145 healthy controls. The most common symptoms associated with metastatic cancer were vomiting, low back pain, loss of appetite, and shoulder pain (range of

ORs from 1.3 to 5.3). Groin pain and pleural disease were also associated but very rare.

Intelligence gathering

One topic expert noted the relevance of the shared decision-making process when discussing PSA test with patients.

Impact statement

The guideline recommends referral for suspected cancer in men if their prostate feels malignant on digital examination. We identified evidence supporting this recommendation with studies reporting a PPV of rectal examination above 3%. We identified studies assessing alarm symptoms in different types of cancer, including prostate cancer. However, no specific results on prostate cancer were described in the abstracts. A topic expert highlighted the relevance of the shared decision-making process when discussing PSA test with patients. The shared decision-making process is relevant to NICE guideline NG12. Recommendations in this area are included in the patient information and support section of the guideline. Also, NICE is currently developing a [shared decision-making guideline](#) which will provide useful recommendations in the area.

New evidence is unlikely to change guideline recommendations.

[Bladder cancer](#)

Surveillance proposal

The section of the guideline on [bladder cancer](#) should not be updated.

2019 surveillance summary

A SR assessed the predictive value of alarm symptoms of bladder or renal cancer in primary care [Schmidt-Hansen M et al. 2015]. A total of 11 studies (3 451 675 patients) were included. The symptom with the highest PPV was haematuria in adults (5.1%), followed by anaemia in males (1.4%). The results

showed that the PPV of haematuria was higher in males and increased with age. Limited data were available on symptom combinations (no further details were reported in the abstract). Authors concluded that haematuria is the symptom that should warrant further investigation. We identified one study published before this SR, so the results are not summarised [Price ST et al. 2014].

A cohort of 6,264 patients from 493 GP practices in 6 different European countries assessed the role of abdominal symptoms in suspected abdominal cancer [Holtedahh K et al. 2018]. Over a 10-day period, people consulting with abdominal pain to the GP practices were included and then followed-up 8 months later. Rectal bleeding was the single symptom with the highest adjusted hazard ratio (adjusted by sex and age) of abdominal cancer. Haematuria, rectal bleeding, and involuntary weight loss as single symptoms had PPVs >3%. Findings showed that irregular bleeding symptoms (rectal bleeding, genital bleeding, and macroscopic haematuria) have a high specificity for CRC, uterine and bladder cancer. Authors concluded that abdominal pain is related to any abdominal cancer.

One observational study assessed the predictive value of symptoms for different cancers [van Boven K et al. 2017]. It was a retrospective analysis of a cohort of patients over 45 years in primary care in Netherlands (118,219 patient-years analysed). The study focused on alarm symptoms defined by the Dutch Cancer Society and Cancer Research UK. Only symptoms spontaneously mentioned by patients in the clinical appointment were included. The PPV for diagnosing cancer in patients referring haematuria was 2.2%. The type of cancer linked to this symptom was not specified in the abstract.

Intelligence gathered

A topic expert highlighted a lack of detail in NICE guideline NG12 on the pathway for patients whose symptoms do not meet the criteria for a suspected cancer referral for bladder cancer. The issue is causing variability in the clinical practice. They mentioned that in some cases the referral was downgraded to routine or in others they were rejected by some units. So,

more clarity is needed in this area to reduce variability and improve the implementation of the guidance.

Impact statement

The current guideline recommends a suspected cancer referral in patients aged 45 and over with unexplained visible haematuria (without urinary tract infection [UTI]) or visible haematuria that persist or recurs after successful treatment of UTI. It also recommends in people aged 60 and over a referral for bladder cancer if they have unexplained non-visible haematuria and dysuria or raised white cell count on a blood test. In these patients, a non-urgent referral is recommended if they have a recurrent or persistent unexplained UTI. Evidence identified during this surveillance review specific for bladder shows that haematuria has a PPV >3%. Evidence on other symptoms and combination of symptoms was also identified, but it showed PPV<3% or it was not specific for bladder cancer. Topic experts highlighted that more guidance is needed in cases where the criteria for referral are not met. The [safety netting section](#) includes recommendations for those cases in which symptoms associated with an increased risk of cancer are presented but do not meet the criteria for referral or other investigative action. We did not identify evidence in any other symptom with a high enough PPV for bladder cancer to warrant a change in the current recommendations.

New evidence is unlikely to change guideline recommendations.

Renal cancer

Surveillance proposal

The section of the guideline on [renal cancer](#) should not be updated.

2019 surveillance summary

SR assessed the predictive value of alarm symptoms of bladder or renal cancer in primary care [Schmidt-Hansen M et al. 2015]. A total of 11 studies

(3,451,675 patients) were included. The symptom with the highest combined PPV was haematuria in adults (5.1%), followed by anaemia in males (1.4%). The results showed that the PPV of haematuria was higher in males and increased with age. Limited data were available on symptoms combinations. Authors concluded that presence of haematuria should warrant further investigation in patients.

A cohort of 6,264 patients from 493 GP practices in 6 different European countries assessed the role of abdominal symptoms in suspected abdominal cancer [Holtedahh K et al. 2018]. Over a 10-day period, people consulting with abdominal pain to the GP practices were included and then followed 8 months later. Rectal bleeding was the single symptom with the highest adjusted hazard ratio (adjusted by sex and age) of abdominal cancer. Haematuria, rectal bleeding, and involuntary weight loss were single symptoms with a PPVs >3%. Macroscopic haematuria was strongly related with bladder and renal cancer.

Intelligence gathering

No relevant information was identified for this section of the guideline

Impact statement

The current guideline recommends a suspected cancer referral pathway in patients aged 45 and over with unexplained visible haematuria (without UTI) or visible haematuria that persist or recurs after successful treatment of UTI. Evidence identified during this surveillance review specific for bladder and renal cancer shows that haematuria has a PPV >3%. Evidence on other symptoms and combination of symptoms was also identified, but it showed PPV<3% or it was not specific for renal cancer. We considered that the evidence identified does not have an impact on current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

Testicular cancer

Surveillance proposal

The section of the guideline on [testicular cancer](#) should not be updated.

2019 surveillance summary

A case-control study assessed the clinical features of testicular cancer in primary care analysing data of 1,398 cases aged 17 and over (4,956 matched cases) included in the Clinical Practice Research Datalink database in the UK [Shephard EA et al. 2018]. Testicular swelling, testicular lump, and scrotal swelling were independently associated with testicular cancer. A testicular lump was the symptom with the highest PPV (2.5%). The PPV of combining testicular lump with testicular swelling was 17% and combining testicular lump with testicular pain was 10%. Authors highlighted that testicular pain may be linked to cancer. They suggest an ultrasound may be useful to rule out testicular cancer in cases where the cause of testicular swelling is uncertain. Authors concluded that the results support current guideline recommendations.

Intelligence gathering

Topic experts highlighted the results of the Shephard EA et al. 2018 study and suggested that the recommendation needs to be reviewed to include its findings, particularly those related to ultrasound, testicular pain, and persistent scrotal swellings.

Impact statement

In the original guideline, no evidence was identified in this area. The guideline committee considered, based on their clinical experience, that non-painful enlargement or change in shape or texture of the testis were alarm symptoms of testicular cancer. Results from one study identified through the surveillance review indicated that a testicular lump was the only symptom with a PPV over 3%. The combination of a testicular lump with testicular pain and testicular lump with testicular swelling had PPVs above the 3% threshold. These combinations are broadly covered in the current recommendations. In the current guideline, direct access to ultrasound scan for testicular cancer is

recommended in men with unexplained or persistent testicular symptoms. Authors of the observational study identified suggest that in cases where the cause of testicular swelling is uncertain, an ultrasound scan may be useful to rule out testicular cancer.

New evidence is unlikely to change guideline recommendations.

[Penile cancer](#)

Surveillance proposal

No new information on [penile cancer](#) was identified at this surveillance review.

[1.7 Skin cancers](#)

[Malignant melanoma of the skin cancer](#)

Surveillance proposal

The section of the guideline on [malignant melanoma of the skin cancer](#) should not be updated.

2019 surveillance summary

A Cochrane review assessed the diagnostic accuracy of visual inspection for the diagnosis of melanoma in adults [Dinnes J et al. 2018]. A total of 51 cohort studies were included. They compared visual inspection (in-person or image-based) with histological confirmation or clinical follow-up. It is unclear in the abstract if the relevant studies identified were conducted in primary care settings. The risk of bias for most of the studies included was unclear. Findings suggested that an in-person assessment performed better than an image-based assessment. Sensitivities (ranged from 76.7% to 92.4%) and specificities (range from 79.7% to 98.3%) depending on prior testing of the participants, referral to secondary care or lesions selected for excision.

Authors reported limitations in their analysis, mainly due to a lack of data reported in the studies included. They concluded that visual inspection is relevant in the assessment of skin lesions, but it cannot be used as the only tool given the risk of missing positive cases.

A similar Cochrane review assessed the accuracy of dermoscopy in the diagnosis of melanoma in adults [Dinnes J et al. 2018]. A total of 103 cohort studies were included. The studies compared dermoscopy (with or without visual inspection) with histological confirmation of clinical or follow-up were included. It is unclear in the abstract if the relevant studies identified were conducted in primary care settings. The studies included had different type of bias and the main limitations identified were in the selection of participants, reproducibility of diagnostic thresholds, and unclear observer expertise. An in-person diagnosis had a higher accuracy compared with image-based assessments. Dermoscopy had a higher accuracy than visual inspection alone. The accuracy improves with the experience of the evaluator. The use of published algorithms in dermoscopy does not improve the accuracy of the results. Authors concluded that dermoscopy has an important role in the diagnosis of melanoma, mainly if it is done by experienced health professionals. There is limited data in primary care settings but dermoscopy is a valuable tool for trained users to assess skin cancer lesions.

Intelligence gathering

No relevant information was identified for this section of the guideline

Impact statement

Evidence identified support the use of visual inspection and dermoscopy in the assessment of suspicious skin lesions in primary care.

New evidence is unlikely to change guideline recommendations.

Squamous cell carcinoma

Surveillance proposal

The section of the guideline on [squamous cell carcinoma](#) should not be updated.

2019 surveillance summary

A Cochrane review assessed the accuracy of visual inspection and dermoscopy in the diagnosis of basal cell carcinoma (BCC) and cutaneous squamous cell carcinomas (CSCC) in primary and secondary care settings [Dinnes J et al. 2018]. A total of 24 cohort studies were included. Most of the studies included had issues related to the applicability of the results, selection of participants, reproducibility of diagnostic thresholds, and unclear observer expertise, among others. Focusing on CSCC findings, authors highlighted that given the limited evidence available, the accuracy of dermoscopy and visual inspection in the diagnosis of CSCC could not be assessed, so no conclusion were drawn in this area.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

Dermoscopy is not currently included as part of the tools used to assess people with a skin lesion that raises the suspicion of squamous cell carcinoma in primary care. We identified one SR assessing the accuracy of visual inspection and dermoscopy in the diagnosis of keratinocyte skin cancers; however, given the limited evidence identified the authors of the study could not draw any conclusion in this area.

New evidence is unlikely to change guideline recommendations.

Basal cell carcinoma

Surveillance proposal

The section of the guideline on [basal cell carcinoma](#) should not be updated.

2019 surveillance summary

A Cochrane review assessed the accuracy of visual inspection and dermoscopy in the diagnosis of basal BCC and CSCC [Dinnes J et al. 2018]. A total of 24 cohort studies were included. Most of the studies included had issues related to the applicability of the results, selection of participants, reproducibility of diagnostic thresholds, and unclear observer expertise, among others. Findings suggested that dermoscopy is more accurate than visual inspection alone in the diagnosis of BBC when used by specialists, but it is unclear if it still being the case when used by GPs in primary care. Authors highlighted that given the lack of data reported they could not evaluate the role of prior testing, observer expertise, or the use of algorithms or checklists in this area. Authors concluded that dermoscopy has a relevant role in the diagnosis of BBC when used alongside visual inspection and an assessment of the risk factors for keratinocyte cancer.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

Dermoscopy is not currently included as part of the tools used to assess people with a skin lesion that raises the suspicion of BCC. The evidence identified during this surveillance review showed that the diagnostic accuracy of the use of dermoscopy alongside visual inspection in the diagnosis of BCC in primary care is unclear. So, these findings do not currently support the inclusion of dermoscopy in the diagnosis of BCC and CSCC.

New evidence is unlikely to change guideline recommendations.

[1.8 Head and neck cancers](#)

[Laryngeal cancer](#)

Surveillance proposal

The section of the guideline on [laryngeal cancer](#) should not be updated.

2019 surveillance summary

A case-control study assessed alarm symptoms of laryngeal cancer in primary care. The study analysed the data registered in the Clinical Practice Research Datalink from patients 40 years and over attending GP services in the UK [Shephard EA et al. 2019]. A total of 806 cases were matched with 3,559 controls. Hoarseness, sore throat, dysphagia, otalgia, re-attendance for dyspnoea, mouth symptoms, recurrent chest infection, insomnia, and raise of inflammatory markers were the alarm symptoms associated with laryngeal cancer. None of the symptoms had a PPV above 3%. The symptom with the highest predictive value was hoarseness (2.7%). The combinations of symptoms were also evaluated, including the combination of sore throat with either dysphagia, dyspnoea or otalgia having PPVs >5% and not currently included in NICE recommendations.

Intelligence gathering

Topic experts highlighted that the symptoms included in the recommendations need to be updated. Intelligence gathered after the publication of the guideline included correspondence from an expert highlighting issues related to the current pathway proposed in the guideline for head and neck cancers. An analysis of local data (Dorset data from 2008-2018, n=846 patients) showed that pharyngeal cancer was the most common subgroup of cancer diagnosed, followed by oral cancer and laryngeal cancer. A neck lump was a symptom most commonly presented in pharyngeal cancer compared with oral and laryngeal cancer in the population assessed.

Impact statement

No primary care evidence was identified in this area to inform guideline recommendations. The guideline committee, based on their clinical

experience, considered that hoarseness and unexplained lump were symptoms indicative of laryngeal cancer. Data from a single observational study described other symptoms associated with laryngeal cancer, but all of them had PPVs below the 3% threshold. Hoarseness was the symptom with the highest PPV (2.7%). Hoarseness is included in the current recommendations. Symptom combinations with a PPV >5% were also identified in the observational study. In the original guideline, results from case-control studies were regarded with caution because this type of design has been shown to be associated with an overestimation of test accuracy parameters compared with studies that incorporate random or consecutive patient selection. Given this limitation and that no other studies were identified, we considered that the evidence is limited to warrant an update of the recommendation. It was noted by one of the topic experts that a neck lump is a symptom more commonly related to other types of head and neck cancers. However, we did not identify any new evidence in this area.

New evidence is unlikely to change guideline recommendations.

Oral cancer

Surveillance proposal

The section of the guideline on [oral cancer](#) should not be updated.

2019 surveillance summary

No new evidence was identified in this surveillance review.

Intelligence gathering

Intelligence gathered after the publication of the guideline included correspondence from a GP, highlighting that throat pain is a relevant symptom of oral cancer not currently included in the recommendations. We also received a correspondence highlighting issues related to the current pathway proposed in the guideline for head and neck cancers. An analysis of local data (Dorset data from 2008-2018, n=846 patients) showed that pharyngeal cancer was the most common subgroup of cancer diagnosed, followed by oral cancer and laryngeal cancer. A neck lump was a symptom most commonly presented

in pharyngeal cancer compared with oral and laryngeal cancer in the population assessed.

NICE guideline NG12 recommends urgent referrals for assessment for possible oral cancer by a dentist. One of the topic experts consulted in this surveillance review mentioned that it would be more convenient to refer patients for assessment by a dental surgeon rather than a community dentist. It was noted the difficulty to communicate with community dentists in an auditable way.

It was also highlighted that human papillomavirus (HPV) was an area of interest in head and neck cancers.

Impact statement

Throat pain was suggested as an important symptom linked to oral cancer. However, throat pain is a symptom that is more likely to be caused by other conditions than oral cancer. It was also suggested to refer patients for assessment to dental surgeons instead of the community dentists. Finally, it was noted that a neck lump was not a common symptom in oral cancer. However, we did not identify any evidence in any of the areas described above to warrant an update of the recommendations. We did not identify new relevant evidence on HPV and head and neck cancers.

New evidence is unlikely to change guideline recommendations.

[Thyroid cancer](#)

Surveillance proposal

No new information on [thyroid cancer](#) was identified at this surveillance review.

1.9 Brain and central nervous system cancers

Adults

Surveillance proposal

This section of the guideline on [brain and central nervous system cancers in adults](#) should not be updated.

2019 surveillance summary

A SR assessed the performance of alarm symptoms for the diagnosis of brain and central nervous system (BCNS) cancer in primary care [Schmidt-Hansen M et al. 2016]. A total of 6 studies (159,938 patients) were included. Results showed very low PPVs in adults and children. The PPV of new-onset seizure was 2.3% in patients aged 60-69 years, dropping to around 1% in those above aged 18 or plus. Symptom combinations were also evaluated, but they obtained very low PPVs as well. Authors concluded that all the symptoms but new-onset seizure in those aged 60-69 years have small predictive values. For the assessment of BCNS cancer, they suggested that there is a need for a broad approach not based on symptoms. However, the cost-effective implications of such a strategy need to be investigated.

A study published after this SR analysed the data of 266 of brain tumour cases included in the National Audit of Cancer Diagnosis in Primary Care [Ozawa M. et al. 2018]. The results showed that the most common symptoms of presentation were focal neurology deficit, then fits, faints or falls; and headache. Patients presenting with headache as a single symptom or memory complaints were more likely to have a delay in the diagnosis of brain cancer.

Intelligence gathered

One of the topic experts highlighted that optometry services could be added to the referral pathway to assess the presence of papilloedema.

Impact statement

In the original guideline, none of the symptoms identified in the evidence had a PPV above 3%. The guideline committee agreed, using their clinical

experience that a progressive sub-acute loss of central neurological function was an important symptom of brain cancer. This symptom was included in the recommendation for referral to an urgent MRI scan of the brain (or CT scan if MRI is contraindicated). We did not identify new single symptoms with a PPV exceeding the 3% threshold for referral. It is considered that the evidence identified does not have an impact on the current recommendation.

New evidence is unlikely to change guideline recommendations.

Children and young people

Surveillance proposal

This section of the guideline on [brain and central nervous system cancers in children](#) should not be updated.

2019 surveillance summary

A SR assessed the performance of alarm symptoms for the diagnosis of BCNS cancer in primary care [Schmidt-Hansen M et al. 2016]. A total of 6 studies (159,938 patients) were included. Results showed very low PPVs in adults and children. In children, the symptom with the highest PPV was seizures. Seizures in children had a positive value of around 0.03% across the different age groups assessed (0-14 years 0.02%, 15-24 years 0.024%). Symptom combinations were also evaluated, but they obtained very low PPVs as well. Authors concluded that all the symptoms have small predictive values. For the assessment of BCNS cancer, they suggested that there is a need for a broad approach not based on symptoms, but the cost-effective implications of such a strategy need to be investigated.

Impact statement

In the original guideline, none of the symptoms identified had a PPV above 3%. The guideline committee considered based on their clinical experience that a new abnormal cerebellar or other central neurological function in this

population were symptoms of brain cancer that need a very urgent specialist assessment. We did not identify new single symptoms with a PPV exceeding the 3% threshold for referral. It is considered that the evidence identified does not have an impact on the current recommendation.

New evidence is unlikely to change guideline recommendations.

1.10 Haematological cancers

Leukaemia in adults

Surveillance proposal

This section of the guideline on [leukaemia in adults](#) should not be updated.

2019 surveillance summary

An observational study assessed the symptoms presented one year before the diagnosis of chronic and acute leukaemia in adults in primary care in the UK [Shephard EA et al. 2016]. A total of 4,655 cases were analysed (number of controls not reported in the abstract). The PPVs were not >1% for any single symptom or combination of symptoms. Ten symptoms were independently associated with chronic leukaemia and 13 symptoms with acute leukaemia (details not reported in the abstract). Patients diagnosed with chronic leukaemia were more likely to present lymphadenopathy, weight loss, and bruising (ORs ranged from 2.3 to 22) than controls. Nosebleeds and bleeding gums, fever, and fatigue were independently associated with acute leukaemia (ORs ranged from 4.4 to 5.7).

Intelligence gathering

No relevant information was identified for this section of the guideline

Impact statement

Similar to the original guideline, we did not identify symptoms with a PPV of 3% or above in this surveillance review. The recommendation (and the

symptoms included in it) was based on committee clinical experience. Given that none of the symptoms described in the study identified through surveillance had PPVs above 3%, we consider that the evidence identified does not have an impact on the current recommendation.

New evidence is unlikely to change guideline recommendations.

[Leukaemia in children and young people](#)

Surveillance proposal

No new information on [leukaemia in children and young people](#) was identified at this surveillance review.

[Myeloma](#)

Surveillance proposal

This section of the guideline on [myeloma in adults](#) should not be updated.

2019 surveillance summary

A case-control study assessed the role of different blood tests in the diagnosis of myeloma in primary care in the UK [Koshiaris C et al. 2018]. Data of symptoms and blood test results (up to 5 years before diagnosis) from 2,073 cases and 12,157 matched controls were analysed and LRs were calculated. Data was extracted from the Clinical Practice Research Datalink. Raised plasma viscosity, erythrocyte sedimentation rate, and C-reactive protein all have positive LRs above 1.2 (range 1.2 to 2.0). Normal levels of haemoglobin, calcium and creatinine had negative LRs between 0.42 to 0.81. The combination of normal results for haemoglobin, calcium and plasma viscosity had the lowest negative LR (0.06), and the combination of normal haemoglobin levels with plasma viscosity had a negative LR of 0.12. Authors concluded that the combination of normal haemoglobin plus plasma viscosity

or erythrocyte sedimentation rate is good for ruling out myeloma. Plasma viscosity or erythrocyte sedimentation are also good for ruling myeloma in or out. A similar study assessed the symptoms presented by patients before the diagnosis of myeloma using data from the General Practice Research Database in the UK [Shepard EA et al. 2015]. The study analysed 2,073 cases and 12,157 matched controls including patients 40 years and over. The main symptoms identified as independently associated with myeloma were raised calcium levels, cytopenia, raised inflammatory markers, raised mean corpuscular volume, weight loss, nosebleeds, rib pain, nausea, chest infection, and shortness of breath but PPVs were below 1%. The combination of some symptoms with leucopenia or hypercalcaemia increased the PPVs over 10%. Those symptoms were not described in the abstract.

An observational study assessed the symptoms presenting 2-years prior to the diagnosis of myeloma in 110 patients [Glodschmidt N et al. 2016]. The setting was not specified in the abstract. Cases were matched with patients without cancer but with back pain. Cases were more likely to have fatigue, weight loss, anaemia, and abnormal erythrocyte sedimentation rate and creatinine levels. These symptoms were identified as independent predictors of myeloma.

One study evaluated the calcium levels of 54,267 patients and assessed the number of cancers diagnosed in the following year [Hamilton F et al. 2014]. The results were obtained from a database of health electronic records in primary care. Hypercalcaemia had a PPV for cancer of 11.5% in males and 4.1% in females. The type of cancers identified was not described in the abstract of the study.

Intelligence gathering

No relevant information was identified for this section of the guideline

Intelligence gathering

A topic expert highlighted the relevance of testing both plasma electrophoresis and Bence-Jones protein in myeloma. The topic expert also noted that there is an increase of the evidence available around the role of serum light chains test in this area.

Impact statement

Similar to the evidence identified in the original guideline, evidence identified during this surveillance review shows that different single alarm symptoms for myeloma have PPVs below 3%. Their PPVs increased if they were combined with hypercalcaemia and leucopenia. In the original guideline, based on committee experience, 4 tests were considered to increase the likelihood of diagnosing myeloma and therefore recommended for use: full blood count, calcium level, and testing for plasma viscosity or erythrocyte sedimentation rate. Evidence identified assessing the role of these tests in the diagnosis of myeloma in primary care show that plasma viscosity and erythrocyte sedimentation rate are good tests to rule in and out myeloma, and the combination of normal results of haemoglobin plus plasma viscosity or erythrocyte sedimentation rate are good options to rule out myeloma. It is considered that the current evidence supports guideline recommendations.

New evidence is unlikely to change guideline recommendations.

[Non-Hodgkin's lymphoma in adults](#)

Surveillance proposal

The section of the guideline on [non-Hodgkin's lymphoma in adults](#) should not be updated.

2019 surveillance summary

A case-control study assessed the risk of non-Hodgkin lymphoma in symptomatic patients in primary care settings in the UK [Shepard EA et al. 2015]. Symptoms presented 1 year before diagnosis from 4,362 cases (40 years old and over), and 19468 matched controls were analysed. Data were extracted from the Clinical Practice Research Datalink. A total of 20 symptoms were independently associated with non-Hodgkin's lymphoma including lymphadenopathy, head and neck mass, other mass, weight loss, and abdominal pain which had the highest risk of non-Hodgkin lymphoma (ORs

ranged from 2.5 to 263). In people 60-year-old and over, lymphadenopathy had a PPV of 13%. PPVs over 2% were identified for symptom combinations including weight loss and repeated back pain or raised gamma globulin levels.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

New evidence identified supports the inclusion of lymphadenopathy as an important symptom of non-Hodgkin's lymphoma. In the current recommendation, other symptoms like fever, night sweats, shortness of breath, pruritus or weight loss need to be considered alongside lymphadenopathy or splenomegaly. Of these symptoms, only weight loss (combined with other symptoms) was mentioned in the abstract of the study identified. In the results of this study, head and neck mass, other mass, or abdominal pain were also symptoms associated with non-Hodgkin's lymphoma. However, given that it was a single case-control study and no data on PPVs were reported in the abstract, it was considered that the evidence was limited to warrant an update of the recommendations.

New evidence is unlikely to change guideline recommendations.

[Non-Hodgkin's lymphoma in children and young people](#)

Surveillance proposal

No new information on [non-Hodgkin's lymphoma in children and young people](#) was identified at this surveillance review.

[Hodgkin's lymphoma in adults](#)

Surveillance proposal

This section of the guideline on [Hodgkin's lymphoma in adults](#) should not be updated.

2019 surveillance summary

A case-control study assessed the risk of Hodgkin's lymphoma in adults (aged 40 years and over) in primary care in the UK. A total of 283 cases and 1,237 controls were included, and symptoms presenting a year before diagnosis were analysed [Shephard EA et al. 2015]. Lymphadenopathy, head and neck mass, other mass, thrombocytosis, raised inflammatory markers, and low full blood count were independently associated with Hodgkin's lymphoma. In people aged 60 years and over, lymphadenopathy had a PPV of 5.6%.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

The new evidence identified supports the current recommendation on considering referral for Hodgkin's lymphoma in adults in people presenting with unexplained lymphadenopathy.

New evidence is unlikely to change guideline recommendations.

[Hodgkin's lymphoma in children and young people](#)

Surveillance proposal

No new information was identified at this surveillance review.

[1.11 Sarcomas](#)

[Bone sarcoma in adults](#)

Surveillance proposal

No new information on [bone sarcoma in adults](#) was identified at this surveillance review.

[Bone sarcoma in children and young people](#)

Surveillance proposal

No new information on [bone sarcoma in children and young people](#) was identified at this surveillance review.

[Soft tissue sarcoma in adults](#)

Surveillance proposal

No new information on [soft tissue sarcoma in adults](#) was identified at this surveillance review.

[Soft tissue sarcoma in children and young people](#)

Surveillance proposal

No new information on [soft tissue sarcoma in children and young people](#) was identified at this surveillance review.

1.12 Childhood cancers

Neuroblastoma

Surveillance proposal

No new information on [neuroblastoma](#) was identified at this surveillance review.

Retinoblastoma

Surveillance proposal

No new information on [retinoblastoma](#) was identified at this surveillance review.

Wilms' tumour

Surveillance proposal

No new information on [Wilms' tumour](#) was identified at this surveillance review.

1.13 Non-site-specific symptoms

Symptoms of concern in children and young people

Surveillance proposal

No new information was on [symptoms of concern in children and young people](#) was identified at this surveillance review.

Symptoms of concern in adults

Surveillance proposal

This section of the guideline on [symptoms of concern in adults](#) should not be updated.

2019 surveillance summary

A SR assessed the predictive value of weight loss for cancer in primary care [Nicholson BD et al. 2018]. Twenty-five observational studies were included; only 4 studies measured the weight directly. Weight loss was associated with prostate, colorectal, lung, gastroesophageal, pancreatic, non-Hodgkin's lymphoma, ovarian, myeloma, renal, and biliary cancers. The PPV was above 3% in those aged 60 years and more.

Intelligence gathering

Topic experts noted that there was new evidence on weight loss and suspected cancer.

Impact statement

The current guideline recommends assessing people with unexplained weight loss because it is a symptom of several cancers. Topic experts also noted that new evidence identified supports these recommendations.

New evidence is unlikely to change guideline recommendations.

1.14 Patient information and support

Surveillance proposal

This section of the guideline on [patient information and support](#) should not be updated.

2019 surveillance summary

One study assessed the patient's preferences in diagnostic investigations for prostate cancer in primary care [Martins T et al. 2015]. An electronic survey assessing the preferences for prostate cancer investigations in 555 men (45 years and over) using hypothetical scenarios with different risk levels of prostate cancer was conducted in 4 GP practices in the UK. Although more than 80% of participants opted for an investigation, the results showed black males were less likely to opt for it than white males at any risk level.

Intelligence gathering

No relevant information was identified for this section of the guideline.

Impact statement

New evidence identified showed the relevance of considering patient preferences in the diagnostic process for prostate cancer in primary care, as well as engaging with them considering any relevant factors such as health beliefs and concerns. The patient information and support section in NG12 provides important recommendations about the discussion of patients' preferences, needs and information to support them during the decision-making process and referral pathway. It also links to the patient experience in adult NHS services which provide additional guidance in this area supporting patient's engagement with healthcare services.

New evidence is unlikely to change guideline recommendations.

1.15 Safety netting

Surveillance proposal

No new information was identified at any surveillance review.

1.16 The diagnostic process

Surveillance proposal

This section should not be updated.

2019 surveillance summary

An observational study assessed the impact of the urgent referral pathway in primary care on cancer survival in the UK [Moller HG et al. 2015]. A total of 215,284 patients with a cancer diagnosis in 2009 were included and followed-up for 4 years until 2013. Three characteristics were independently associated with a reduced mortality: the use of urgent referral, a standardised referral ratio and the detection rate. Authors concluded that an urgent referral pathway is useful to improve cancer survival in patients.

On study assessed the impact of undertaking additional primary care investigations in patients who do not fulfil the criteria for urgent referral in the UK [Rubin GP et al 2015]. Data of 5,036 cases of lung, colorectal, stomach, oesophagus, pancreas and ovarian cancer obtained from the English National Audit of Cancer Diagnosis in Primary Care were analysed. Findings showed that investigations in primary care are associated with a delay in the referral for specialist assessment, and this was independent of the symptoms presented by the patients. Authors suggested that arrangements to improve intervals between ordering investigations, obtaining and assessing the results is relevant to reduce late referrals to secondary care.

Use of health electronic records and decision support tools

Health electronic records

A study assessed the feasibility and validity of using electronic health records to identify patients with small cell lung cancer (SCLC) in primary care [Cea Soriano L et al. 2019]. Code sets and free text related to SCLC included in the Health Improvement Network database in the UK were used to identify the patients. A manual review was used to validate the data. A total of 3,530 cases of SCLC were identified. Most of the patients had a symptom suggestive of lung cancer recorded. The most prevalent one was a respiratory tract infection, followed by cough, chest pain, abdominal pain and back pain.

Authors concluded that the use of health electronic records appears to be a good method to identify cancer patients, but more research is needed. A feasibility study explored the use of information technologies to identify patients with CRC [Kidney EB et al. 2015]. NICE recommendations on urgent referral were included in a clinical audit software in 20 GP practices in the UK, so patients between 60-79 years could be identified and assessed by a GP. Almost 20 thousand records were analysed, 809 people were identified at risk; most of them with anaemia and rectal bleeding. One third of the people identified at risk needed further clinical review. A total of 10 CRCs were identified. Authors concluded that information technologies could be a tool to identify patients with CRC.

Decision support tools

A cross-sectional postal survey in the UK assessed the availability and use of decision support tools in primary care [Price S et al. 2019]. GP practices were randomly selected and a total of 476 GPs, from the 4,600 GPs and registrars invited to participate, responded to the survey. A third of the GP practices had access to cancer decision support tools. The results showed that the use of these tools is not associated with an earlier diagnosis. Authors concluded that decision support tools are not largely used in the UK, and more robust studies are needed in this area.

A qualitative study evaluated the implementation and usefulness of electronic decision support tools for skin cancer in primary care in the UK [Pannebakker MM et al. 2019]. GPs and patients' perspectives were assessed using face-to-face semi-structured interviews. A total of 28 participants were included (14 in each group). Most of the GPs perceived that these tools are useful, mainly in cases of borderline decisions, but it could also increase unnecessary referrals to specialised care. None of the patients interviewed knew that the tools were used during their GP appointments.

A qualitative study assessed the views of GP on using electronic risk assessment tools for lung cancer and CRC [Dikomitis L et al. 2015]. A total of 23 phone interviews were conducted. GP considered that the use of electronic risk assessment tools is useful but could lead to a 'fatigue' effect if they are continually receiving alerts. A similar study explored GPs' experiences of

using cancer risk assessment tools (lung and CRC) [Green T et al 2015]. The results highlighted that these tools are useful but could be more straightforward to implement if they are perceived as a support tool not as a replacement for clinical judgement.

Intelligence gathering

Topic experts highlighted the use of electronic health records in general practice for risk assessment for cancer for patients in primary care as an ongoing research area that is relevant for this guideline.

Impact statement

New evidence identified support the use of the two-week referral pathway for suspected cancer. Evidence from an observational study suggest that investigations in primary care are associated with a delay in the referral for specialist assessment. NICE guideline NG12 recommends that arrangements need to be in place to support non-urgent referrals or any additional investigations, so it does not have an impact on the time to be referred to secondary care. The use of electronic health records and decision support tools is an emerging area of interest. It was also highlighted by topic experts. Evidence identified suggest that information technology tools could be useful to identify patients with cancer, but more research is needed to assess the effectiveness of those interventions in suspected cancer.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered in the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

Pharyngeal cancer

Surveillance proposal

This section should not be added.

2019 surveillance summary

Intelligence gathered after the publication of the guideline included correspondence from a GP highlighting issues related to the current pathway proposed in the guideline for head and neck cancers. An analysis of Dorset data from 2008-2018 (n=846 patients) showed that pharyngeal cancer was the most common subgroup of cancer diagnosed, followed by oral cancer and laryngeal cancer. A neck lump was a symptom most commonly presented in pharyngeal cancer than in oral and laryngeal cancer. It was also highlighted that the current recommendations do not consider pharyngeal cancer even though the number of HPV-related oropharyngeal cancers is raising.

Intelligence gathering

One of the topic experts highlighted that symptoms of hypopharyngeal cancer, especially the main symptom, odynophagia is not included in the guideline. This symptom was also noted by another topic expert who also mentioned other relevant symptoms such as lateralising throat pain, and difficulty in swallowing/obstruction.

Impact statement

One of the topic experts noted that pharyngeal cancer is a relevant head and neck cancer and it was missed in NICE guideline NG12. In the original guideline, the guideline committee agreed to cover the top 30 cancers according to the incidence plus any additional cancers that had been covered by the previous version of the guideline but did not appear in the top 30. The reason behind that was that it was not possible for the guideline to cover all cancers. Focusing on head and neck cancers, the [latest release of Cancer registration statistics in England \(2017\) from the Office for National Statistics](#) showed that most of the head and neck cancers occur in the larynx, followed by oral cancer [ONS 2017]. We did not identify new relevant evidence on pharyngeal cancer. Another topic expert highlighted that odynophagia, the main symptom of hypopharyngeal cancer was not included in the guideline. Odynophagia pain is a symptom that is more likely to be caused by other conditions than oral cancer. Other symptoms were also highlighted but we did

not identify any new evidence in the area. So, it is considered that there is no new evidence to warrant an addition of this cancer to the guideline.

Rapid diagnosis centres

Surveillance proposal

This section should not be added.

2019 surveillance summary

No new evidence was identified in this surveillance review.

Intelligence gathering

One of the topic experts highlighted the emergence of rapid diagnostic centres and the need for guidance in this area.

Impact statement

We did not identify any new evidence in this area, so we considered that this section should not be added.

Research recommendations

[2.1 Age thresholds in cancer](#)

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

[2.2 Primary care testing](#)

Summary of findings

A case-control study assessed the role of inflammatory markers for cancer diagnosis in primary care [Watson J et al. 2019]. A total of 160,000 patients with data on inflammatory markers and 40,000 untested controls were

analysed. The data was extracted from the Clinical Practice Research Datalink and Cancer Registry database and the 1-year cancer incidence calculated. The inflammatory markers assessed were C-reactive protein, erythrocyte sedimentation rate and plasma viscosity. The 1-year cancer incidence was 3.53% in patients with abnormal inflammatory markers. Abnormal inflammatory markers were associated with an increased risk of cancer. The risk increases with age and in males and decreases when the markers go back to normal levels. Authors concluded that inflammatory markers have a role in the diagnosis of cancer, but they have low sensitivity values, so they cannot be used for ruling out cancer.

One study assessed the value of adding a urinary biomarker of bladder cancer (Cxbt) and imaging in the assessment of patients with haematuria in primary care [Davidson PJ et al. 2019]. The data of 571 patients attending primary care with haematuria were included. A theoretical model was developed in which patients with positive results in the initial assessment were referred to specialised care and cystoscopy. Results showed that the model had a sensitivity and specificity over 97%.

Topic experts consulted during this surveillance review highlighted that this is a relevant area for primary care. Only two observational studies were identified in the current surveillance review. One of them concluding that inflammatory markers are relevant in the diagnosis of cancer, but they cannot be used for ruling out cancer. Another small observational study assessed the role of a urinary biomarker in bladder cancer. It used a theoretical model to assess the accuracy of the test. Although the results showed that the test performed well, given the limitations of the study design it is considered that the evidence provided is limited to be considered in an update of the guideline.

2.3 Cancers insufficiently researched in primary care

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

2.4 Patient experience

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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