in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

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ERRATUM TO

Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: A systematic review and cost-effectiveness analysis

1. The following study:

   Parente F, Marino B, Ilardo A, Fracasso P, Zullo A, Hassan C, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol* 2012;24(10):1145-52.

   was erroneously included in the systematic review. This study did not use HM-JACKarc (as specified in the scope and protocol for this assessment), but rather used an older version (HM-JACK). HM-JACK and HM-JACKarc are different analytical systems and use different sampling devices. HM-JACK is no longer available in Europe. The above study has therefore been removed from the results sections of the systematic and added to the list of excluded studies.

   Corrected versions of pages 4, 18, 40-46, 48, 66-69, 71 and 158 are copied below.

   The study has been deleted from Appendix 2 and Appendix 3. All publications relating to this study have added to Appendix 4 (excluded studies). A revised version of Appendix 4 is provided below.

1. Abstract

Background

Colorectal cancer (CRC) is the third most common cancer in the UK. Symptoms, such as rectal bleeding, unexplained weight loss, anaemia, abdominal pain and altered bowel habit can be associated with CRC, but will usually have another explanation. Faecal immunochemical tests (FIT) can detect blood in stools that is not visible to the naked eye. These tests may help to determine which patients are most likely to benefit from further investigation.

Objectives

To assess the clinical and cost effectiveness of FIT as triage test for people presenting in primary care, with low risk symptoms for CRC.

Methods

Twenty-four resources were searched to March 2016. Review methods followed published guidelines. Studies were assessed for quality using QUADAS-2 and PROBAST. The bivariate model was used to estimate summary sensitivity and specificity for meta-analyses involving four or more studies, otherwise random effects logistic regression was used. The health economic analysis considered the long-term costs and quality adjusted life years (QALYs) associated with different faecal occult blood tests and no triage (referral straight to colonoscopy). The de novo model consisted of a diagnostic decision model, a Markov model to estimate long-term costs and QALYs associated with the treatment and progression of CRC and a Markov model to estimate the QALYs associated with no CRC.

Results

Ten studies (25 publications and two unpublished manuscripts) were included in the clinical effectiveness review. When FIT testing was based on a single faecal sample and a threshold of 10 µg Hb/g faeces was applied, the sensitivity estimates for OC-Sensor, 92.1% (95% CI: 86.9 to 95.3%), and HM-JACKarc, 100% (95% CI: 71.5 to 100%), indicated that these tests may be useful to rule-out CRC. Specificity estimates were 85.8% (95% CI: 78.3 to 91.0%) and 76.6% (95% CI: 72.6 to 80.3%), respectively. Triage using FIT at this threshold could rule-out CRC and avoid colonoscopy in approximately 75% of symptomatic patients. In addition, data from our systematic review suggest that between 22.5% and 93% of patients with a positive FIT test and no CRC will have other significant bowel pathologies.

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Assessment of cost effectiveness

A de novo health economic model was developed to explore the cost effectiveness of using FIT for Hb as a triage step in the investigation of symptomatic people presenting in primary care who are at low risk of CRC. The cost effectiveness of FIT was compared to guaiac faecal occult blood tests (gFOBT) and to no triage (referral straight to colonoscopy). The model consists of three parts, a decision model reflecting the diagnosis of colorectal cancer, a Markov state-transition model to estimate long-term costs and effects (life years and QALYs) associated with the treatment and progression of CRC and a Markov state-transition model to estimate the life years and QALYs associated with those who do not have CRC. The following strategies were included in the main economic analysis:

- Triage using OC-Sensor at a threshold of 10 µg Hb/g faeces
- Triage using HM-JACKarc at a threshold of 10 µg Hb/g faeces
- Triage using gFOBT
- No triage (referral straight to colonoscopy)

The model was largely based on that used in the Suspected cancer: recognition and referral NICE guideline (NG12) but with diagnostic accuracy data coming from the systematic review used to inform the assessment of effectiveness. Where available, data was obtained from the most recent published sources, although expert opinion was required to inform some parameters. Any differences in costs between the tests in patients without CRC were assumed to occur only in the first year. Any differences in life expectancy between tests for patients without CRC were assumed to be only due to difference in mortality due to colonoscopy/CTC. A negative FIT or gFOBT results in a watchful waiting strategy, in which a colonoscopy/CTC will be performed when symptoms persist, which is assumed to occur with all CRC patients. All unit cost data on FIT were obtained from manufacturers where supplied.

The uncertainty about the model input parameters and the potential impact on the model results were explored by scenario, one-way deterministic and probabilistic sensitivity analyses.

Results

Assessment of clinical effectiveness

Ten studies (25 publications and two unpublished manuscripts) were included in the systematic review. The main potential sources of bias in the included studies related to patient spectrum and patient flow (numbers of patients who did not return a FIT sample or who were subsequently

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Quality assessment was undertaken by one reviewer and checked by a second reviewer (MW and SL), any disagreements will be resolved by consensus or discussion with a third reviewer.

The results of the quality assessments are summarised and presented in tables and graphs in the results of the systematic review and are presented in full, by study, in Appendix 3.

3.1.5 Methods of analysis/synthesis

Sensitivity and specificity were calculated for each set of 2×2 data. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive hierarchical summary receiver operating characteristic curves for meta-analyses involving four or more studies.[46-48] This approach allows for between-study heterogeneity in sensitivity and specificity, and for the trade-off (negative correlation) between sensitivity and specificity commonly seen in diagnostic meta-analyses. For meta-analyses with fewer than four studies we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression.[49] Heterogeneity was assessed visually using summary receiver operating characteristic plots and statistically using the variance of logit (sensitivity) and logit (specificity) , where "logit" indicates the logistic function: the smaller these values the less heterogeneity between studies. Analyses were performed in Stata 10 (StataCorp LP, College Station, Texas, USA), using the *metandi* command. For analyses that would not run in Stata we used MetaDisc.[50]

Studies were grouped by FIT assay type, by target condition and by threshold. We compared the accuracy of different FIT assays by tabulating summary estimates from analyses for commonly used thresholds. Stratified results tables receiver operating characteristic ROC space plots were used to illustrate the variation of test performance by threshold.

We used summary receiver operating characteristic (ROC) plots to display summary estimates from analyses which included a minimum of four data points.

3.2 Results of the assessment of clinical effectiveness assessment

The searches of bibliographic databases and conference abstracts identified 5,782 references. After initial screening of titles and abstracts, 113 were considered to be potentially relevant and ordered for full paper screening; of these 21 were included in the review,[12, 51-70] Additionally, four presentations were obtained through contact with a clinical expert (CF).[71-74] One unpublished manuscript was provided, through NICE, by the manufacturer of FOB Gold (personal communication: e-mail from Philippa Pinn, Sysmex UK Ltd, via. Rebecca Albrow, Technical Lead, NICE

to Marie Westwood, Project lead, KSR Ltd, 21/06/2016). Additional unpublished work was provided by the clinical expert (CF) (personal communication, ahead of publication: e-mail from Callum Fraser, Honorary Consultant Clinical Biochemist, NHS Tayside, to Marie Westwood, Project lead, KSR Ltd, 10/07/2016). All potentially relevant studies cited in other documents supplied by the test manufacturers had already been identified through other sources. Figure 1 shows the flow of studies through the review process, and Appendix 4 provides details, with reasons for exclusions, of all publications excluded at the full paper screening stage. In total there were ten included studies derived from 27 articles.

Seventy-four articles were excluded after full text screening. Twelve articles could not be obtained[75-86] and one further article was published in Russian with no English abstract.[87]

We contacted the authors of publications that reported data from studies with mixed populations (symptomatic, screening and surveillance patients) to request separate data for the symptomatic subgroup; where no additional data were obtained, these studies were excluded (see Appendix 4). The authors of two studies[55, 57] provided additional test accuracy data, which were included in our review.

3.2.1 Overview of included studies

Details of the ten included studies and their associated references are provided in Table 3. Additional data were supplied by the authors of two studies.[55, 57] In the case of Terhaar sive Droste 2011,[57] the authors provided overall data for symptomatic study from the master database, which holds data for all of their publications (personal communication: e-mail from Sietze van Turenhout to Marie Westwood 12/06/2016). The results section of this report cites studies using the primary publication and, where this is different, the publication (shown in bold in Table 3) in which the referenced data were reported.

Five studies reported accuracy data for the OC-Sensor assay; one used the iO analyser (Eiken Chemical Co., Tokyo, Japan),[51] one used the OC-Sensor Diana automated immunoturbidimetric analyser (Eiken Chemical Co., Tokyo, Japan),[12] two used the MICRO desktop analyser (Eiken Chemical Co., Tokyo, Japan),[52, 57] and one did not report the analyser used.[54] Three studies reported accuracy data for the HM-JACKarc automated system (Kyowa Medex, Tokyo, Japan).[55, 56, 74] The remaining two studies reported accuracy data for the FOB Gold assay; one used the Roche Modular P/917 analyser (Roche Diagnostics Ltd, West Sussex, UK),[53] and the other used the SENTiFIT 270 analyser (Sentinal Diagnostics, Milan, Italy), (personal communication: e-mail from Philippa Pinn, Sysmex UK Ltd, via. Rebecca Albrow, Technical Lead, NICE to Marie Westwood, Project lead, KSR Ltd, 21/06/2016). There

were no studies, using the Ridascreen Hb or the Ridascreen Hb/Hp complex assays, which met the inclusion criteria for this assessment. None of the included studies reported data comparing different FIT assays, or comparing one or more FIT assays to a gFOBT method. All studies included in our systematic review were diagnostic cohort studies which reported data on the diagnostic accuracy of FIT, where the target condition was CRC or advanced neoplasia (defined as CRC or high risk adenoma [HRA]). Five studies reported additional accuracy data various non-malignant and composite target conditions.[12, 51, 55, 57, 74]

Six of the diagnostic accuracy studies included our systematic review also reported uptake rates for participants invited to provide a sample for FIT testing.[12, 51, 52, 54, 55, 74]

No RCTs or CCTs were identified; no studies provided data on patient-relevant outcomes following FIT compared to gFOBT or no faecal occult blood testing.

All ten included studies were conducted in Europe; one in England,[74] three in Scotland,[12, 51, 55] three published studies[52, 54, 56] and one unpublished study (personal communication: e-mail from Philippa Pinn, Sysmex UK Ltd, via. Rebecca Albrow, Technical Lead, NICE to Marie Westwood, Project lead, KSR Ltd, 21/06/2016) in Spain, and one each in the Netherlands,[57] and Slovenia.[53] Three studies were publically funded,[51, 52, 54] five studies reported receiving some funding from manufacturers (including supply of test kits, reagents and analysers),[12, 54-56, 74] one study did not report details of funding,[53] and the unpublished study was conducted at the request of the test manufacturer.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, and FIT assay used and reference standard are reported in the data extraction tables presented in Appendix 2 (Tables a and b).

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Figure 1: Flow of studies through the review process

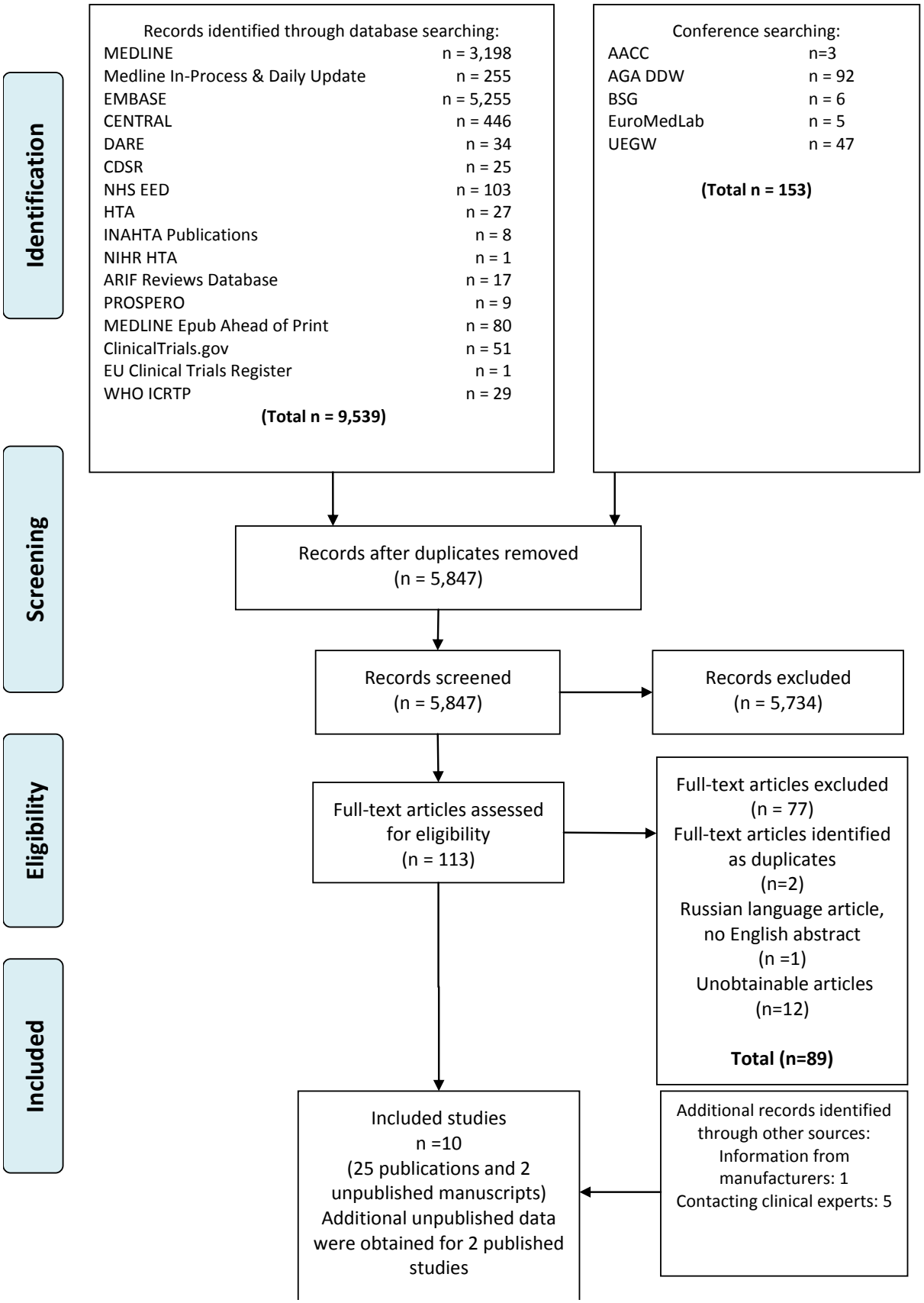

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Table 3: Details of included studies

Details	Country	N	Reference standard
HM-JACKarc			
Thomas 2016[74]	England	450	CT/ Colonoscopy.
Godber 2016[55] Macdonald 2015 [70]; Godber 2014 [64]	Scotland	507	Colonoscopy
Auge 2016[56] Auge 2014[65]; Auge 2015[71]	Spain	208	Colonoscopy
FOB Gold system			
Krivec 2011[53]	Slovenia	NR	Colonoscopy
[redacted]ǂ	[redacted]	[redacted]	[redacted]
OC-sensor			
McDonald 2012[12]	Scotland	280	Colonoscopy and flexible sigmoidoscopy.
Mowat 2015[51] Steele 2014[73]	Scotland	755	Colonoscopy
Rodríguez-Alonso 2015[52]	Spain	1003	Colonoscopy
Cubiella 2014 (COLONPREDICT)[54] Diaz Ondina 2014[60]; Cubiella 2015[72] Unpublished data‡	Spain	787	Colonoscopy
Terhaar sive Droste 2011[57] Oort 2011[62]; van Turenhout 010[68]; van Turenhout 2014[58]; Imperiale 2012[61]; van Turenhout 011[67]; Oort 2010[63]; van Turenhout 2012[59]; Larbi 2012[66]; van Turenhout 2010[69]	The Netherlands	2058	Colonoscopy

ǂ personal communication: e-mail from Philippa Pinn, Sysmex UK Ltd, via. Rebecca Albrow, Technical Lead, NICE to Marie Westwood, Project lead, KSR Ltd, 21/06/2016.

‡ personal communication, ahead of publication: e-mail from Callum Fraser, Honorary Consultant Clinical Biochemist, NHS Tayside, to Marie Westwood, Project lead, KSR Ltd, 10/07/2016

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3.2.2 Study quality

All studies included in this systematic review were diagnostic cohort studies. The methodological quality of these studies was assessed using the QUADAS-2 tool[44] (summarised in Table 4 and Figure 2). One of these studies[52] and an additional report[72] and un-published paper (personal communication, ahead of publication: e-mail from Callum Fraser, Honorary Consultant Clinical Biochemist, NHS Tayside, to Marie Westwood, Project lead, KSR Ltd, 10/07/2016) linked to a second study[54] reported the development and validation of risk prediction scores that included FIT, in addition to test accuracy results. These studies were assessed using PROBAST (Table 5) as well as QUADAS-2. The full QUADAS-2 assessments for each study are provided in Appendix 3a and PROBAST assessment results are provided in Appendix 3b.

Two studies were reported only as conference abstracts, with limited descriptions of methods.[53, 74]

Two studies were rated as 'low' risk of bias for all domains.[54, 56] [redacted] The main potential sources of bias, across the included studies, concerned flow and timing, and application of the index test. Three studies were rated as 'high' risk of bias on the flow and timing domain because some patients who returned a sample for FIT or who agreed to participate in the study were subsequently excluded from the analysis: Mowat 2015[51] excluded 11% of participants who returned a FIT sample because they were not subsequently referred to secondary care or because the referral was cancelled; Thomas 2016[74] excluded 12.5% of participants who returned a FIT sample (no reasons for exclusion were reported); McDonald 2012[12] excluded 41% of people who originally agreed to participate in the study (38% did not return a FIT sample before endoscopy and 3% completed FIT but not endoscopy). [redacted]

All of the included studies were rated as having 'high' concerns about applicability with respect to participants. This was because no study reported data specific to the population defined in the scope

for this assessment (people presenting, in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1]). Only one study was conducted in a primary care setting,[51] reporting that FIT was ordered by GPs at the point of referral to secondary care. All studies included some participants who had symptoms that may be considered to be associated with a higher probability of CRC and which are components of the criteria for two week referral as defined in NG12[1] (e.g. rectal bleeding). In addition, although all of the included studies were conducted in Europe, only four were conducted in the UK (one in England[74] and three in Scotland[12, 51, 55]) Given that population studies have shown variation in faecal Hb concentrations, and hence potential variation in optimal thresholds for FIT, across different geographic location,[88, 89] this may limit the applicability of our findings to UK settings.

Table 4: QUADAS-2 results for studies of FIT assays

	RISK OF BIAS				APPLICABILITY CONCERNS		
Study	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT	INDEX TEST	REFERENCE STANDARD
Auge 2016[56]	+	+	+	+	-	+	+
Cubiella 2014 (COLONPRED ICT)[54]	+	+	+	+	-	+	+
Godber 2016[55]	+	+	?	+	-	+	+
[redacted]	*	*	*	*	*		
Krivec 2011[53]	?	-	?	?	-	+	-
McDonald 2012[12]	+	+	?	-	-	+	?
Mowat 2015[51]	+	+	+	-	-	+	+
Rodríguez-Alonso 2015[52]	?	+	+	+	-	+	+
Terhaar sive Droste 2011[57]	+	+	+	?	-	+	+
Thomas 2016[74]	?	+	?	-	-	+	+
+ Low Risk; - High Risk; ? Unclear Risk							

* Personal communication: e-mail from Philippa Pinn, Sysmex UK Ltd, via. Rebecca Albrow, Technical Lead, NICE to Marie Westwood, Project lead, KSR Ltd, 21/06/2016

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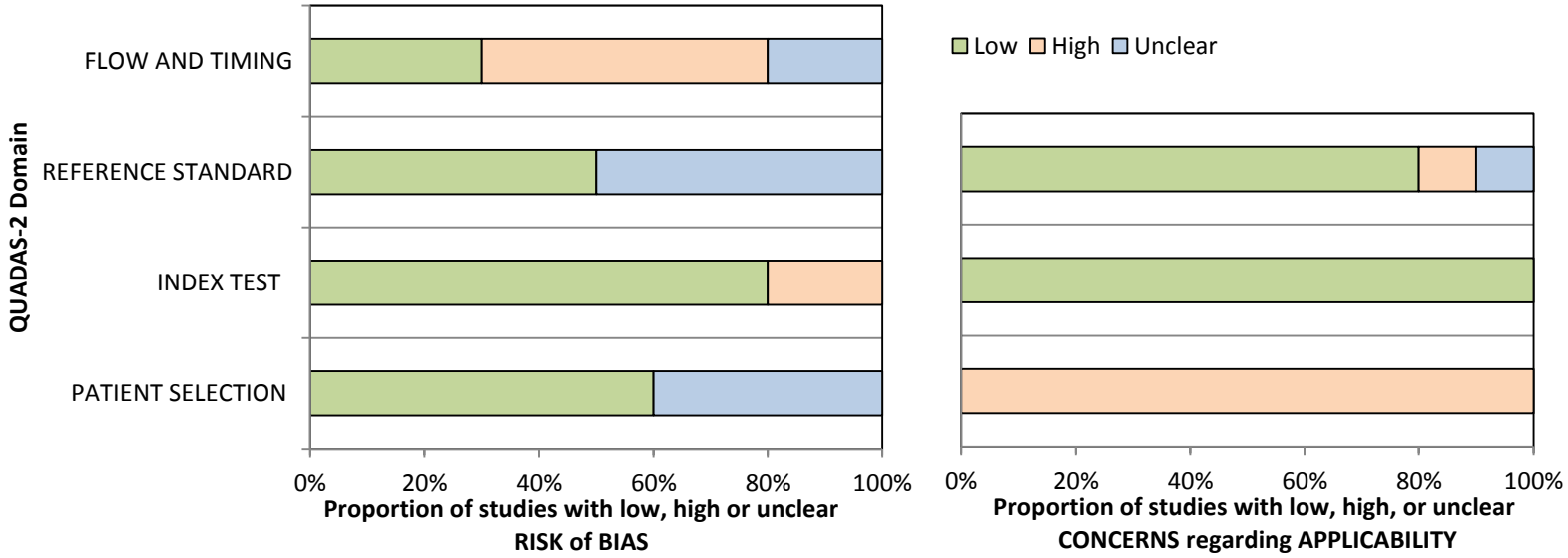
Figure 2: Summary of QUADAS-2 results for studies of FIT assays



3.2.4 Diagnostic peformance of the HM-JACKarc FIT assay

Details of HM-JACKarc studies

Three diagnostic cohort studies,[55, 56, 74] reported in seven publications, [55, 56, 64, 65, 70, 71, 74] provided data on the diagnostic performance of the HM-JACKarc FIT assay. Two studies reported accuracy data, where CRC was the specified target condition[55, 74] The prevalence of CRC, diagnosed at colonoscopy, was 2.2% in the Godber 2016 study,[55] and 4.9% in Thomas 2016.[74] One of the CRC studies[55] and one additional study[56] also reported data for the composite target condition of advanced neoplasia (CRC or HRA). Each of the studies used a different definition of HRA; Auge 2016[56] defined HRA based on size, morphology or number of lesions (any lesion ≥10 mm in diameter or with villous architecture or high grade dysplasia, or ≥3 non-advanced adenomas) and Godber 2016[55] defined higher risk adenoma, based on size or number of lesions, using a combination of the British Society of gastroenterology (BSG) categories high risk (≥5 adenomas or ≥3 adenomas at least one of which is ≥10 mm diameter) and intermediate risk (3-4 small adenomas or at least one adenoma ≥10 mm diameter).[90] Two studies reported additional accuracy data for various non-malignant and composite target conditions.[55, 74]

No study reported data specific to the population defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1]). No studies were conducted in a primary care setting; all three studies were conducted in outpatient clinics.[55, 56, 74] One study stated that FIT was requested after referral for colonoscopy[55] and in the remaining two studies, the timing of FIT in relation to colonoscopy referral was unclear.[56, 74] One study, reported as a conference abstract, stated that only symptomatic patients were included, but did not report details of presenting symptoms.[74] The remaining two studies included patients who had been referred for colonoscopy,[55, 56] and one recorded presenting symptoms (reason for referral).[55] Both of the studies that reported presenting symptoms included some participants who had symptoms may be considered to be associated with a higher probability of CRC and which are components of the criteria for two week referral as defined in NG12[1] (e.g. rectal bleeding). Presenting symptoms included rectal bleeding/haematochezia, abdominal pain, change in bowel habit, constipation or diarrhoea, anaemia and weight loss. The median age of study participants was 67 years,[74] 63 years[56] and 59 years[55] and the overall age range was 16 to 93 years. There were no data linking presenting symptoms to age. One study reported data on the effects of the sex of participants on the accuracy of HM-JACKarc for the detection of advanced neoplasia.[56] Full details of participant characteristics are provided in Appendix 2, Table a.

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All three studies reported data on the accuracy of HM-JACKarc FIT using a single faecal sample. [55, 56, 74] One study also compared the accuracy of single versus double sampling FIT for the detection of advanced neoplasia.[56]

Two studies reported information about uptake rates in participants invited to provide a sample for FIT. [55, 74]

Accuracy of HM-JACKarc for the detection of CRC

Two studies reported data on the accuracy of HM-JACKarc FIT using a single faecal sample and thresholds of 10 µg Hb/g faeces,[55] and 7 µg Hb/g faeces.[74] Full test performance results are provided in Table 11. There was little variation in test performance between the 7 and 10 µg Hb/g faeces thresholds; the sensitivity estimates were 100% and 91.3%, respectively, and the corresponding specificity estimates were 76.6% and 79.2%.[55, 74] As with the OC-Sensor FIT assay, the optimal test performance (maximising both sensitivity and specificity) appeared to occur with thresholds of 7 or 10 µg Hb/g faeces; none of the HM-JACKarc studies reported test performance characteristics for any detectable Hb. Using test performance data from Godber 2016,[55] and a CRC prevalence estimate of 2.2% taken from the same study, to consider the outcome of testing for a hypothetical cohort of 1,000 patients indicates that no CRCs would be missed using the 10 µg Hb/g faeces threshold, but 229 unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and that all colonoscopies conducted in patients without CRC are considered unnecessary); CRC would be correctly ruled out in 750 people (Figure 8). Please see subsequent sections for information on other significant bowel pathologies that may be detected by FIT and hence may form part of the false positive or 'unnecessary colonoscopy' population.

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Figure 8: Testing outcomes for a hypothetical cohort of 1,000 patients using HM-JACKarc the 10 µg Hb/g faeces threshold for the target condition CRC

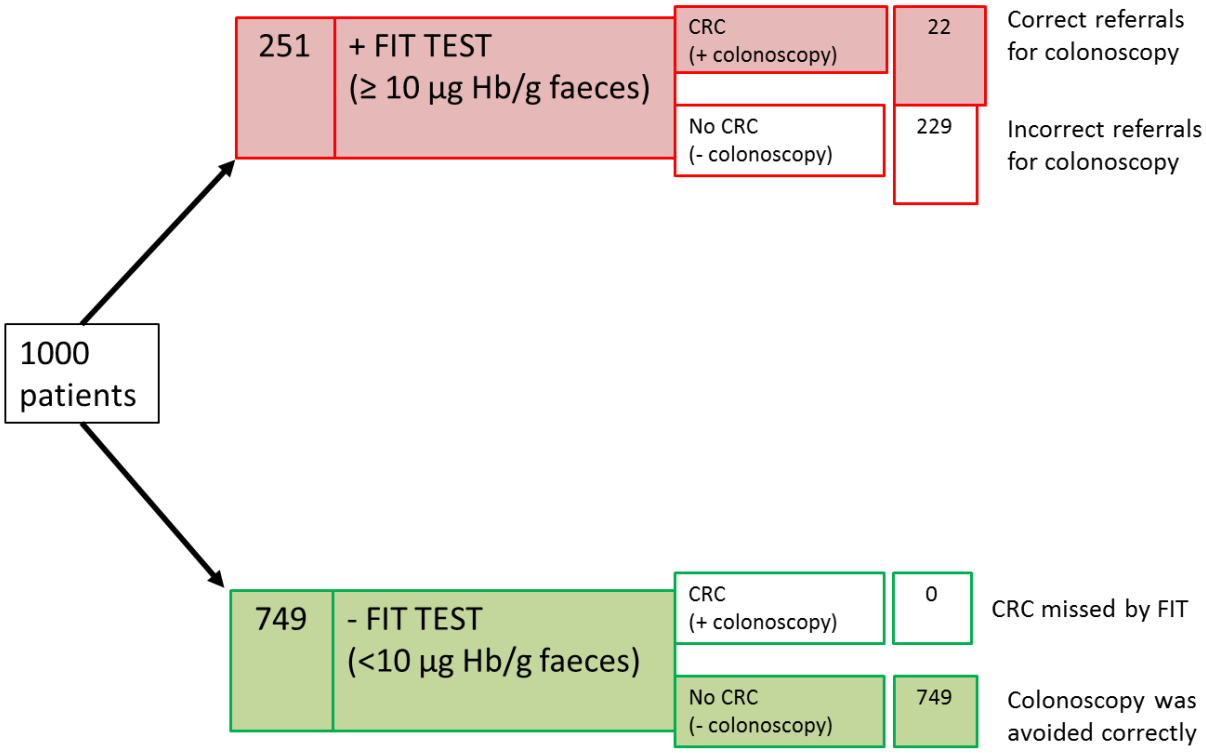
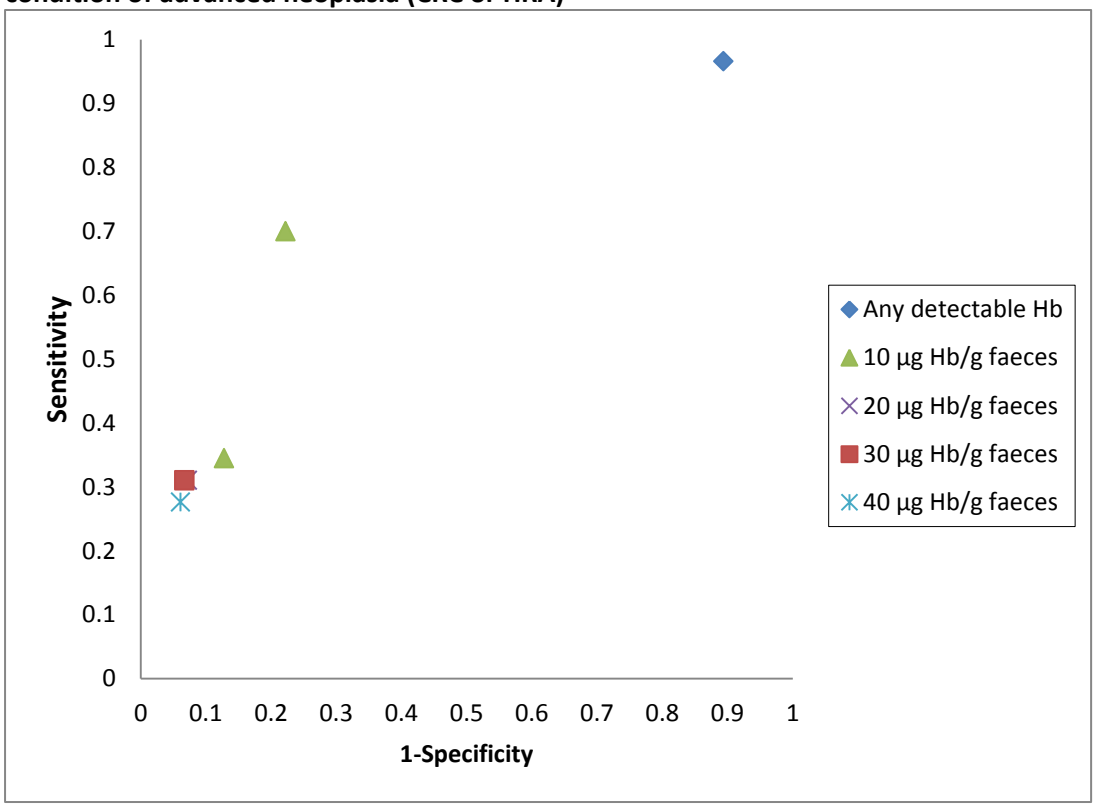


Figure 9: ROC space plot for the HM-JACKarc assay using different thresholds for the target condition of advanced neoplasia (CRC or HRA)



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Accuracy of HM-JACKarc for the detection of advanced neoplasia (CRC or HRA)

Two studies reported data on the accuracy of HM-JACKarc FIT using a single faecal sample, where the target condition as expanded to include CRC or HRA.[55, 56] Two studies, Godber 2016[55] and Auge 2016[56], assessed the diagnostic performance of the 10 µg Hb/g faeces threshold for different definitions of this expanded target condition (see *Details of HM-JACKarc Studies*, above); these two studies reported very different estimates of sensitivity (70% and 34.5%, respectively). In addition to the difference in the definition of HRA, the Auge 2016 study differed from Godber 2016 in that it included some patients who were undergoing colonoscopy for polyp surveillance and excluded people with GI bleeding or active rectal bleeding; the prevalence of CRC in Auge 2016 was the lowest of any study included in this review (0.96%).[56] Auge 2016 reported test performance characteristics using a range of thresholds; sensitivity decreased and specificity increased with increasing threshold and the 'any detectable Hb' threshold was associated with high sensitivity (96.6%) and very low specificity (10.6%).[56] Full test performance results for all thresholds evaluated in individual studies are provided in Table 12. The variation in test performance characteristics according to the threshold used is illustrated in a ROC space plot (Figure 9).

Based on the data from Godber 2016, expanding the target condition from CRC only to include CRC or HRA, resulted in an increase in prevalence from 2.2% to 5.9%.[55] Using test performance data from this study, and an estimate for the prevalence of advanced neoplasia of 5.9%, to consider the outcome of testing for a hypothetical cohort of 1,000 patients indicates that, applying FIT at the 10 µg Hb/g faeces threshold would result in 21 advanced neoplasias being missed. Since data indicate that no CRCs would be missed at this threshold (see previous section), it may be assumed that the missed cases would all be higher risk adenomas. Using the 10 µg Hb/g faeces threshold, 205 unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and that all colonoscopies conducted in patients without at least higher risk adenoma are considered unnecessary); CRC and higher risk adenoma would be correctly ruled out in 727 people (Figure 10).

Data from Auge 2016 indicated that, in this population (CRC prevalence <1%), high sensitivity (good rule-out performance) could only be achieved using the 'any detectable Hb' threshold; the sensitivity at this threshold was 96.6%.[56] This study also compared the performance of double versus single sampling and found that 100% sensitivity could be achieved by using the highest value from two consecutive samples and the 'any detectable Hb' threshold.[56] The use of two consecutive samples increased sensitivity, compared to single sampling, at all thresholds, but sensitivity remained low

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Table 11: Accuracy of HM-JACKarc for the detection of CRC using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total N	2x2 Data	Sensitivity % (95% CI)	Specificity % (95% CI)
Godber 2016[55~]	≥10	11	0	116	380	507	reported	100 (71.5, 100)[*]	76.6 (72.6, 80.3)[*]
Thomas 2016[74]	≥7	21	2	89	338	450	calculated	91.3 (79.8, 102.8)	79.2 (75.3, 83)

[~]Personal communication (e-mail from Ian Godber to Marie Westwood 08/06/2016)

[*] Calculated estimate

Table 12: Accuracy of HM-JACKarc for the detection of advanced neoplasia (CRC or high/higher risk adenoma) using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total N	2x2 Data	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable Hb									
Auge 2016[56]	0[*]	28	1	160	19	208	calculated	96.6 (82.8, 93.4)	10.6 (6.9, 15.9)
10 µg Hb/g faeces									
Auge 2016[56]	≥10	10	19	23	156	208	calculated	34.5 (19.9, 52.7)	87.2 (81.6, 91.3)
Godber 2016[55~]	≥10	21	9	106	371	507	reported	70.0 (50.6, 85.3)[**]	77.8 (73.8, 81.4)[**]
Other thresholds									
Auge 2016[56]	≥20	9	20	13	166	208	calculated	31 (17.3, 49.2)	92.8 (88, 95.7)
Auge 2016[56]	≥30	9	20	12	167	208	calculated	31 (17.3, 49.2)	93.3 (88.7, 96.1)
Auge 2016[56]	≥40	8	21	11	168	208	calculated	27.6 (14.7, 45.7)	93.9 (89.4, 96.6)

[*] The limit of detection for the assay is 0.6 µg Hb/g faeces or 0.6 ng/ml buffer

[~]Personal communication (e-mail from Ian Godber to Marie Westwood 08/06/2016)

[**] Calculated estimate

alone.[141] Faecal calprotectin is an inflammatory marker, whilst M2-PK is a key enzyme in tumour metabolism.[141] This study found that, in all cases, the addition of at least one further test to FIT resulted in markedly increased sensitivity and decreased specificity. The sensitivity and specificity estimates for FIT alone and CRC were 61.7% (95% CI: 47.4 to 74.2%) and 88.8% (95% CI: 84.1 to 92.3%); for the combination of FIT and faecal calprotectin these estimates were 90.9% (95% CI: 78.8 to 96.4%) and 35.9% (95% CI; 29.7 to 42.6%), for FIT and M2-PK sensitivity and specificity were 91.5% 995% CI: 80.1 to 96.6%) and 57.1% (95% CI: 50.6 to 63.2%) and for all three markers they were 95.7% (85.7 to 98.8%) and 24.1% (18.8 to 30.2%).[141] Although all sensitivity estimates were generally lower, this pattern was repreated where the target condition was advanced neoplasia.[141] However, the FIT threshold in this study (20 µg Hb/g faeces) was higher than that which the results of our systematic review indicate is likely to be the optimal threshold (10 µg Hb/g faeces or a lower threshold). A second study of accuracy for the target condition of advanced neoplasia, which did not meet the inclusion criteria for this assessment because it used a qualitative FIT method,[142] also found that combining faecal calprotectin with FIT (where a positive result was defined as either or both tests positive) resulted in increased sensitivity and decreased specificity (92% (95% CI: 82 to 97%) and 49% (95% CI: 43 to 54%)) compared to FIT alone (74% (95% CI: 62 to 83%) and 82% (95% CI: 78 to 86%)).[142] The effectiveness of combining other biomarkers with quantitative FIT (at the threshold at which FIT is likley to be used in practice) remains unclear. We did not identify any data about the effects of adding faecal calprotectin (or any other biomarker) to risk scores that include FIT. An un-published study provided AiC (personal communication: e-mail from Karel Moons, Professor of Clinical Epidemiology, University Medical Center, Utrecht, the Netherlands, to Marie Westwood, Project lead, KSR Ltd, 20/06/2016) [redacted] Given the trade-off between ease of use/simplicity and diagnostic performance, the clinical value of including additional variables (e.g. symptoms and further diagnostic tests) in risk scores for CRC and/or other significant bowel disease is likely to require further investigation.

There is uncertainty about downstream consequences of using FIT to triage symptomatic patients in primary care. It can be seen from the findings of our systematic review (see Sections 3.2.3 to 3.2.5) that triage using FIT at thresholds around 10 µg Hb/g faeces has the potential to correctly rule-out CRC and avoid colonoscopy in approximately 75% of symptomatic patients and that this estimate

Appendix 4: Table of excluded studies with rationale

To be included in the review studies had to fulfil the following criteria:

Population:	Adults (≥18 yrs.) presenting with symptoms suggestive of possible CRC
Setting:	Primary care
Index Test:	Quantitative FIT (OC-Sensor, HM-JACKarc, FOB Gold, Ridascreen Hb, Ridacsreen Hb/Hp complex
Reference Standard:	Colonoscopy
Outcome:	Sufficient data to construct 2x2 table of test performance

The table below summarises studies which were screened for inclusion based on full text publication but did not fulfil one or more of the above criteria. Studies were assessed sequentially against criteria; the first criterion failed is classified as the reason for exclusion. The table shows which of the criteria each study fulfilled ("Yes") and on which items it failed ("No"), as well as any which were ("Unclear"). Articles which did not report primary research were not assessed further. Any criteria which are not applicable to a study are marked N/A. Where population was the only reason for exclusion and studies reported a mixed population, authors were contacted to request subgroup data for symptomatic patients; this is noted in the comments column.

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Abdullah M, Simadibrata M, Syam AF, Wijayadi T, Fauzi A, Santi A, et al. The accuracy of fecal immunochemical test in early detection of colorectal cancer. *J Gastroenterol Hepatol* 2010;25:A138	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Qualitative FIT. Population unclear, participants undergoing colonoscopy for any indication
Allison JE, Fraser CG, Halloran SP, Young GP. Comparing fecal immunochemical tests: improved standardization is needed. *Gastroenterology* 2012;142(3):422-4	No						Not primary research
Banaszkiewicz Z, Jawien A, Jarmocik P, Tojek K, Jankowski M, Switonski M. [Evaluation of usefulness of faecal occult blood test. Prospective screening study in patients with colorectal neoplasia]. *Pol Merkuriusz Lek* 2004;17(102):579-82	Yes	Unclear	Unclear	No	Unclear	Unclear	No relevant index test Polish language publication, qualitative FIT
Bjerregaard NC, Tottrup A, Sorensen HT, Laurberg S. Detection of colorectal cancer in symptomatic outpatients without visible rectal bleeding: validity of the fecal occult blood test. *Clin Epidemiol* 2009;1:119-24	Yes	Yes	Yes	No	Yes	Yes	No relevant index test gFOBT only
Bonfrate L, Ruggiero V, Dambrosio P, Castorani L, De Bari O, Larizza M, et al. Double vs. standard fecal occult blood testing (FOBT) in patients with alarm symptoms of colorectal cancer (CRC). *Eur J Clin Invest* 2013;43:71	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test Qualitative FIT
Carroll M, Piggott C, Pearson S, Seaman HE, Bruce H, Halloran SP. An evaluation of quantitative faecal immunochemical tests for haemoglobin [Poster]. *British Society of Gastroenterology Annual Meeting*. Manchester, 2014: 89	Yes	No	Unclear	Yes	No	No	Not a symptomatic population Spiked samples, technical performance only
Castro I, Estevez P, Cubiella J, Hernandez V, Gonzalez-Mao C, Rivera C, et al. Diagnostic performance of fecal immunochemical test and sigmoidoscopy for advanced right-sided colorectal neoplasms. *Dig Dis Sci* 2015;60(5):1424-32	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Average risk cohort of asymptomatic men
Chen JG, Cai J, Wu HL, Xu H, Zhang YX, Chen C, et al. Colorectal cancer screening: comparison of transferrin and immuno fecal occult blood test. *World J Gastroenterol* 2012;18(21):2682-8	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic surveillance. Qualitative FIT

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Chiang TH, Lee YC, Tu CH, Chiu HM, Wu MS. Immunochemical FOBT was accurate for detecting colorectal cancer but less so for other GI lesions. *Ann Intern Med* 2012;156(4):JC2-JC10	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Screening with qualitative FIT
Chiu HM, Wu MS, Lee YC, Liao WC, Wang HP, Lin JT. Fecal immunochemical test has lower performance in detecting early and proximal advanced colorectal neoplasm. *Gastroenterology* 2012;142(5 Suppl 1):S145	Yes	No	No	No	Yes	Yes	Not a symptomatic population Screening population
Cole SR, Upton J, Lane JM, Young GP. A faecal immunochemical test for haemoglobin using a single stool sample is effective for detecting significant colorectal neoplasia. *J Gastroenterol Hepatol* 2009;24:A239	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Unclear population, all patients scheduled for colonoscopy. No relevant FIT
Crouse AL, De Koning L, Sadrzadeh SM, Naugler C. Sensitivity and specificity of community fecal immunotesting screening for colorectal carcinoma in a high-risk Canadian population. *Arch Pathol Lab Med* 2015;139(11):1441-5	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Screening population
Dutta AK, Alagammai P, Chowdhury SD, Chacko A. Preprocedure haemoglobin and fecal occult blood testing for optimising colonoscopy rates in a resource limited setting for diagnosing colonic malignancy. *Gastrointest Endosc* 2012;75(4 Suppl 1):AB325-AB326	Yes	No	Unclear	No	Yes	No	Not a symptomatic population gFOBT only, test performance only reported for combined gFOBT and anaemia
Fenocchi E, Gaggero P, Rondan M, Lopez-Alvarenga JC, Sobrino-Cossio S, Lambert N, et al. Usefulness of the fecal immunochemical test in the detection of advanced adenomas in subjects at average risk for colorectal cancer. *Endoscopia* 2015;27(2):64-68	Yes	Yes	Unclear	Yes	Yes	No	No relevant outcomes Separate data for symptomatic and asymptomatic patients. Reported outcome was mean FIT level for different adenoma sizes
Gillberg A, Ericsson E, Granstrom F, Olsson LI. A population-based audit of the clinical use of faecal occult blood testing in primary care for colorectal cancer. *Colorectal Dis* 2012;14(9):e539-46	Yes	Unclear	Unclear	No	No	Yes	No relevant index test Retrospective study, symptoms data only collected for those patients with a diagnosis of CRC

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Gopalswamy N, Stelling HP, Markert RJ, Maimon HN, Wahlen SD, Haddy RI. A comparative study of eight fecal occult blood tests and HemoQuant in patients in whom colonoscopy is indicated. *Arch Fam Med* 1994;3(12):1043-8	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic, asymptomatic high risk and surveillance. No relevant FIT (gFOBT only)
Greenberg PD, Bertario L, Gnauck R, Kronborg O, Hardcastle JD, Epstein MS, et al. A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol* 2000;95(5):1331-8	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening, history of CRC or polyps, or family history (30% symptomatic). No relevant FIT technology
Haug U, Kuntz KM, Knudsen AB, Hundt S, Brenner H. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. *Br J Cancer* 2011;104(11):1779-85	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Average risk screening population
Hogberg C, Karling P, Rutegard J, Lilja M, Ljung T. Immunochemical faecal occult blood tests in primary care and the risk of delay in the diagnosis of colorectal cancer. *Scand J Prim Health Care* 2013;31(4):209-14	Yes	No	Unclear	Unclear	N/A	No	Patients with an established cancer diagnosis Retrospective study of cancer patients who had received qualitative FIT, reports sensitivity of FIT and delay to diagnosis following a negative FIT
Iwase N, Oya M, Yanagida T, Hirayasu Y, Ishii Y, Kubota T, et al. [Immunological fecal occult blood test in patients with anal diseases]. *Nihon Daicho Komonbyo Gakkai Zasshi* 1995;48(9):1065-1069	Yes	Yes	Unclear	No	Yes	No	No relevant index test Japanese language publication, gFOBT only. Only sensitivity data reported
Jin P, Wu Z, Meng M, Wang X, Gong L, Yu D, et al. Combined fecal transferrin test and immuno fecal occult blood test for detecting colorectal cancer and advanced adenoma in asymptomatic and symptomatic populations. *J Cancer Sci Ther* 2012;4(8):243-248	Yes	Yes	Unclear	No	Yes	No	No relevant index test Qualitative FIT, no accuracy data

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Kalimutho M, Del Vecchio Blanco G, Cretella M, Mannisi E, Sileri P, Formosa A, et al. A simplified, non-invasive fecal-based DNA integrity assay and iFOBT for colorectal cancer detection. *Int J Colorectal Dis* 2011;26(5):583-92	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Qualitative FIT
Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. *Int J Surg* 2013;11(4):329-31	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Qualitative FIT
Kennell M, Antle S, Hammond M, Stone S, Mahar D, Randell E. Evaluation of the analytical and diagnostic performance of the iFOBT NS-Plus system for use in a province-wide colorectal cancer screening program. *Clin Biochem* 2012;45(13-14):1116	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Qualitative FIT
Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003;115(2):111-4	Yes	No	Unclear	No	No	No	Not a symptomatic population Screening with qualitative FIT
Kovarova JT, Zavoral M, Zima T, Zak A, Kocna P, Kohout P, et al. Improvements in colorectal cancer screening programmes - quantitative immunochemical faecal occult blood testing - how to set the cut-off for a particular population. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2012;156(2):143-50	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic, previous CRC, family history (32% symptomatic) – **authors contacted, reply received stating that subgroup data are not available**
Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. *BMJ* 1983;286(6366):673-4	Yes	Yes	Yes	No	No	Yes	No relevant index test gFOBT only. Reference standard proctosigmoidoscopy and double contrast barium enema (colonoscopy in patients with normal findings on these tests who had positive FOBT results)

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Leodolter A, Zielinski D, Vieth M, Labenz J. Comparison of different immunological fobts for colorectal cancer screening: wide range of sensitivity between different rapid tests. *Gastroenterology* 2010;138(5 Suppl 1):S159	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic (approximately 66% symptomatic) – **authors contacted, no reply received**
Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. *Aliment Pharmacol Ther* 2006;23(9):1359-64	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population Asymptomatic screening
Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med* 2007;146(4):244-55	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population symptomatic and asymptomatic screening or high risk (47% symptomatic) – **authors contacted, no reply received**
Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, et al. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. *Am J Gastroenterol* 2009;104(4):933-8	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, increased risk and mildly symptomatic, proportions not specified – **authors contacted, no reply received**
Levy BT, Bay C, Xu Y, Daly JM, Bergus G, Dunkelberg J, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. *J Med Screen* 2014;21(3):133-43	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population (symptomatic, screening or surveillance), proportion not reported. No relevant FIT technology

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Luthgens K, Maier A, Kampert I, Sieg A, Schmidt-Gayk H. Hemoglobin-haptoglobin-complex: a highly sensitive assay for the detection of fecal occult blood. *Clinical Laboratory* 1998;44(7-8):543-551	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Participants from a gastroenterological practice, unclear if symptomatic. Study is of a development version of the test not that which is currently marketed
McDonald R, Tomlins A, Smith S, Harmston C. Outcomes of faecal occult blood tests requested outside the UK National Bowel Cancer Screening Programme. *J Clin Pathol* 2013;66(4):330-4	Yes	Unclear	Unclear	No	N/A	No	No relevant index test Unclear population, survey of testing requests before and after introduction of screening
Miyoshi H, Oka M, Sugi K, Saitoh O, Katsu K, Uchida K. Accuracy of detection of colorectal neoplasia using an immunochemical occult blood test in symptomatic referred patients: comparison of retrospective and prospective studies. *Intern Med* 2000;39(9):701-6	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Qualitative FIT
Narula N, Ulic D, Al-Dabbagh R, Ibrahim A, Mansour M, Balion C, et al. Fecal occult blood testing as a diagnostic test in symptomatic patients is not useful: a retrospective chart review. *Can J Gastroenterol Hepatol* 2014;28(8):421-6	Yes	No	No	No	Yes	Yes	Not a symptomatic population Hospital in-patients, not all symptomatic, type of FOB test not reported
Niv Y, Sperber AD. Sensitivity, specificity, and predictive value of fecal occult blood testing (Hemoccult II) for colorectal neoplasia in symptomatic patients: a prospective study with total colonoscopy. *Am J Gastroenterol* 1995;90(11):1974-7	Yes	Yes	Yes	No	Yes	Yes	No relevant index test gFOBT only
Ogawa M, Iso A, Ootsuka H, Shimizu S, Aoki Y, Tada M, et al. [Clinical evaluation of a new immunological fecal occult blood test]. *Ther Res* 1989;10(2):275-282	Yes	No	Unclear	No	No	Yes	No relevant index test Japanese language publication, qualitative FIT, case-control study
Oono Y, Iriguchi Y, Doi Y, Tomino Y, Kishi D, Oda J, et al. A retrospective study of immunochemical fecal occult blood testing for colorectal cancer detection. *Clin Chim Acta* 2010;411(11-12):802-5	Yes	Yes	Yes	No	Yes	Yes	No relevant index test No relevant FIT technology

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Oort FA, Droste JSTS, Van Der Hulst RW, Van Heukelem H, Loffeld RJ, Wesdorp EC, et al. Flat colonic neoplasia are left undetected by fecal immunochemical tests (FIT) and will be missed in colorectal cancer screening. *Gastroenterology* 2009;136(5 Suppl 1):A113	Yes	Unclear	Unclear	Yes	Yes	No	No relevant outcomes Unclear population, all patients scheduled for colonoscopy. No accuracy data.
Ou CH, Kuo FC, Hsu WH, Lu CY, Yu FJ, Kuo CH, et al. Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. *J Dig Dis* 2013;14(9):474-83	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population (history of CRC or polyp, family history, symptomatic, asymptomatic screening) proportions not reported – **authors contacted, no reply received**
Parente FR, Marino B, Perna F, Saracino IM, Zullo A, Hassan C, et al. Multiple faecal tests (colon panel) for the detection of colon cancer: a new strategy for appropriate prioritization of screening referrals? Preliminary experience in Italy. *Gastroenterology* 2010;138(5 Suppl 1):S192.	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACK (no longer available in Europe) not HM-JACKarc
Parente F, Marino B, Perna F, Saracino I, Zullo A, Hassan C, et al. Multiple faecal tests (colon panel) for the detection of colon cancer: a new strategy for appropriate prioritization of screening referrals? Preliminary experience in Italy. *Dig Liver Dis* 2010;42:S86.	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACK (no longer available in Europe) not HM-JACKarc
Parente F, Marino B, Ilardo A, Fracasso P, Zullo A, Hassan C, et al. A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol* 2012;24(10):1145-52.	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACK (no longer available in Europe) not HM-JACKarc
Piper MA. *Immunochemical versus guaiac fecal occult blood tests*. Chicago, IL: Blue Cross and Blue Shield Association, Technology Evaluation Center, 2004	No						Not primary research Provisional DARE abstract, with no publication details

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Rae AJ, Cleator IGM. The two-tier fecal occult blood test: cost effective screening. *Can J Gastroenterol* 1994;8(6):362-368	Yes	No	Unclear	No	No	No	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening and surveillance, gFOBT only
Rao S, Forbes G, Venugopal K. High yield for advanced colorectal neoplasia (carcinoma and advanced adenoma) detection with community based faecal immunochemical testing. *J Gastroenterol Hepatol* 2014;29:133-134	Yes	No	Unclear	Unclear	Yes	No	Not a symptomatic population Patients referred from primary care because of a positive FIT. FIT method not specified
Rodriguez-Moranta F, Ariza X, Berrozpe A, Vazquez X, Binefa G, Navarro M, et al. Comparative study of guaiac and quantitative immunochemical fecal occult blood test for colorectal neoplasia. Preliminary results. *Gastroenterology* 2009;136(5 Suppl 1):A623	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening, or surveillance (66% symptomatic). Un-specified FIT – **authors contacted, no reply received**
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Quantitative colonoscopic evaluation of relative efficiencies of a quantified immunochemical fecal occult blood test and a sensitive guaiac test for detecting significant colorectal neoplasms. *Gastroenterology* 2009;136(5 Suppl 1):A113	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Unclear population, 'consecutive ambulatory colonoscopy patients, some above average risk'– **authors contacted, no reply received**
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Identification of colorectal adenomas by a quantitative immunochemical faecal occult blood screening test depends on adenoma characteristics, development threshold used and number of tests performed. *Aliment Pharmacol Ther* 2009;29(8):906-17	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and high risk asymptomatic (59% symptomatic) – **authors contacted, no reply received**

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Colonoscopic evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Gastroenterology* 2009;136(5 Suppl 1):A624	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Unclear population, 'consecutive ambulatory colonoscopy patients, some above average risk'– **authors contacted, no reply received**
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, et al. Quantitative colonoscopic evaluation of relative efficiencies of an immunochemical faecal occult blood test and a sensitive guaiac test for detecting significant colorectal neoplasms. *Aliment Pharmacol Ther* 2009;29(4):450-7	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening or high risk (23% symptomatic) – **authors contacted, no reply received**
Rozen P, Comaneshter D, Levi Z, Hazazi R, Vilkin A, Maoz E, et al. Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer* 2010;116(9):2115-25	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population Screening asymptomatic
Sailer M. [A quantitative immunological fecal occult blood test in colorectal neoplasia]. *Coloproctology* 2010;32(1):68-70	No						Not primary research Journal club, screening
Sailer M. [The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer]. *Coloproctology* 2013;35(2):148-150	No						Not primary research Journal club, screening
Sieg A, Scheida M, John MR, Hertel A, Schroter M, Luthgens K, et al. Validity of new immunological human fecal hemoglobin and albumin tests in detecting colorectal neoplasms - an endoscopy-controlled study. *Z Gastroenterol* 1998;36(6):485-90	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Early development paper (not a commercially available test)
Shaw AG, Lund JN, Longman C, Tierney GM, Goddard AF. The misuse of the faecal occult blood test under the lower gastrointestinal two week wait rule. *Colorectal Dis* 2009;11(1):94-6	Yes	Yes	Yes	No	N/A	No	No relevant index test Survey of gFOBT testing prior to referral (no test performance data)

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Symonds EL, Young GP, Osborne JM, Cole SR, Gopalsamy G, Gaur S, et al. Detection of colorectal neoplasia: comparison of a methylated two-gene (BCAT1-IKZF1) blood test with a faecal immunochemical test. *J Gastroenterol Hepatol* 2015;30:83	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population: States 'scheduled for colonoscopy for any reason,' but the objective describes test evaluation in 'a patient population exhibiting the full spectrum of pathology encountered in the colon/rectum'– **authors contacted, no reply received**
Tate JJ, Northway J, Royle GT, Taylor I. Faecal occult blood testing in symptomatic patients: comparison of three tests. *Br J Surg* 1990;77(5):523-6	Yes	Yes	Yes	No	No	Yes	No relevant index test gFOBT only. Patients referred for double contrast barium enema (reference standard), assumed by the authors to be symptomatic
Thomas WM, Hardcastle JD, Jackson J, Pye G. Chemical and immunological testing for faecel occult blood: a comparison of two tests in symptomatic patients. *Br J Cancer* 1992;65(4):618-20	Yes	Yes	Yes	No	Yes	No	No relevant index test Only sensitivity data reported
Tibble J, Sigthorsson G, Foster R, Sherwood R, Fagerhol M, Bjarnason I. Faecal calprotectin and faecal occult blood tests in the diagnosis of colorectal carcinoma and adenoma. *Gut* 2001;49(3):402-8	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, healthy controls, known CRC and referred patients (symptomatic and polyp surveillance, proportions not specified). No relevant FIT technology
Tsumuraya M, Noda A, Tsubura S, Sugimoto K, Minowa M, Seki T, et al. [Comparative clinical study of 'Monohem' and four reagents for faecal occult blood test]. *Ther Res* 1989;10(Suppl 1):87-95	Yes	No	Unclear	No	No	Yes	No relevant index test Japanese language publication, qualitative FIT, case-control study

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
University of Aarhus. A Trial of the Implementation of iFOBT in General Practice. NCT02308384 In: International Clinical Trials Registry Platform [Internet]. Geneva: World Health Organization. 2014 [accessed 9.3.16]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02308384	Yes	Yes	Yes	Unclear	N/A	No	No relevant outcomes Ongoing study, behavioural intervention for general practitioners
University of Malaya. Quantitative Versus Qualitative Fecal Immunochemical Tests (FIT) to Prioritize Urgency of Colonoscopy Referral. NCT02037646 In: International Clinical Trials Registry Platform [Internet]. Geneva: World Health Organization. 2014 [accessed 9.3.16]. Available from: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02037646	Yes	No	No	Unclear	Yes	Yes	Not a symptomatic population Screening study, index test and comparator unclear
Uppsala University. Quantitative Immunochemical Fecal Occult Blood Test in Symptomatic Patients. NCT02491593 In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015 [accessed 9.3.16]. Available from: https://ClinicalTrials.gov/show/NCT02491593	Yes	Yes	Yes	Unclear	Unclear	Yes	No data available Ongoing study, potentially relevant. Unclear intervention, quantitative FIT. Un-specified reference standard
Van Turenhout ST, Van Rossum LG, Oort FA, Laheij RJ, Van Rijn AF, Fockens P, et al. Differences in FIT results between screening and referred colorectal cancer patients are explained by differences in tissue tumor stage. *Gastroenterology* 2010;138(5 Suppl 1):S185	Yes	No	Unclear	Yes	Yes	No	Not a symptomatic population Comparison of stages of CRC between screening detected and symptomatic patients
Viana Freitas BR, Kibune Nagasako C, Pavan CR, Silva Lorena SL, Guerrazzi F, Saddy Rodrigues Coy C, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. *Gastroenterol Res Pract* 2013;2013:384561	Yes	No	No	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic high risk, or surveillance. Qualitative FIT
Vilkin A, Rozen P, Levi Z, Waked A, Maoz E, Birkenfeld S, et al. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol* 2005;100(11):2519-25	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic high risk (approximately 73% symptomatic) – **authors contacted, no reply received**

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Vogel T, Driemel C, Hauser A, Hansmann A, Lange S, Jonas M, et al. [Comparison of different stool tests for the detection of cancer of the colon]. *Dtsch Med Wochenschr* 2005;130(14):872-7	Yes	No	No	No	Yes	Yes	Not a symptomatic population Includes health control participants. No relevant FIT technology
Wakamura K, Kudo SE, Ikehara N, Mori Y, Hayashi S, Takeda K, et al. A prospective evaluation using the colonoscope of the fecal occult blood test-negative colorectal neoplasms in a referral hospital. *Gastrointest Endosc* 2012;75(4 Suppl 1):AB343-AB344	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population (approximately 25% symptomatic). Unspecified FIT method – **authors contacted, reply received: No relevant FIT technology**
de Wijkerslooth TR, Stoop EM, Bossuyt PM, Meijer GA, van Ballegooijen M, van Roon AH, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. *Am J Gastroenterol* 2012;107(10):1570-8	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Asymptomatic screening
Williams JA, Hunter R, Coles ME, Thomas DW, Huber TW. An assessment of an immunochemical test for human haemoglobin in the detection of colonic polyps. *Aust N Z J Surg* 1985;55(5):485-8	Yes	No	Unclear	Unclear	Yes	No	Not a symptomatic population Mixed population symptomatic and asymptomatic, or history of CRC (proportions not reported). FIT type not reported
Wong BC, Wong WM, Cheung KL, Tong TS, Rozen P, Young GP, et al. A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003;18(9):941-6	Yes	No	Unclear	No	Yes	No	Not a symptomatic population Mixed population, symptomatic and asymptomatic surveillance (46% symptomatic). FlexSure OBT & Hemoccult SENSA, no relevant FIT technology. Only sensitivity data reported

Study Details	Primary study	Population	Setting	Index Test	Reference Standard	Outcome	Reason for exclusion and comments
Wong WM, Lam SK, Cheung KL, Tong TS, Rozen P, Young GP, et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. *Cancer* 2003;97(10):2420-4	Yes	No	No	No	Yes	No	Not a symptomatic population Mixed population, symptomatic, polyp surveillance, history of CRC, or family history (37% symptomatic). No relevant FIT technology. Only sensitivity data reported
Woo HY, Mok RS, Park YN, Park DI, Sung IK, Sohn CI, et al. A prospective study of a new immunochemical fecal occult blood test in Korean patients referred for colonoscopy. *Clin Biochem* 2005;38(4):395-9	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic or history of CRC (60% symptomatic) – **authors contacted, no reply received**
Wu D, Luo HQ, Zhou WX, Qian JM, Li JN. The performance of three-sample qualitative immunochemical fecal test to detect colorectal adenoma and cancer in gastrointestinal outpatients: an observational study. *PLoS One* 2014;9(9):e106648	Yes	No	No	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic history of CRC or polyp. Qualitative FIT
Yeasmin F, Ali MA, Rahman MA, Sultana T, Rahman MQ, Ahmed AN. A comparative study of chemical and immunological method of fecal occult blood test in the diagnosis of occult lower gastrointestinal bleeding. *Bangladesh Med Res Counc Bull* 2013;39(2):52-6	Yes	Unclear	Unclear	Unclear	Yes	No	No relevant outcomes Only patients who were positive on either FIT or gFOBT received colonoscopy; the sensitivity and specificity of FIT and gFOBT individually were then assessed against colonoscopy in this pre-selected sample. Unclear whether participants were symptomatic, FIT unspecified