National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Quantitative faecal immunochemical tests to assess people with symptoms, who are at low risk of colorectal cancer, in primary care

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using quantitative faecal immunochemical tests to triage (identify those at greatest risk) low-risk symptomatic populations for suspected colorectal cancer referrals. Several symptoms can suggest colorectal cancer, including rectal bleeding, a change in bowel habits, weight loss, anaemia, abdominal pain, and blood in stools (faeces). Sometimes, blood in stools is not visible (faecal occult blood) so tests are used to detect its presence. These faecal occult blood tests can be used in primary care to assess people who are at a low risk of colorectal cancer and help determine if they should be referred for further investigations. The low-risk symptomatic population for whom faecal occult blood testing is recommended is outlined in NICE's guidance on suspected cancer, and is described in further detail below. Faecal occult blood can be caused by conditions other than colorectal cancer,

so further assessment with a colonoscopy is needed to diagnose colorectal cancer; a positive faecal occult blood test alone cannot be used.

Faecal immunochemical tests, a type of faecal occult blood test, are designed to detect small amounts of blood in stool samples using antibodies specific to human haemoglobin. They have been developed as an alternative to guaiac-based faecal occult blood tests, which involve using chemicals that react with the haem component of haemoglobin in the blood and produce a blue colour change if blood is detected. Sometimes, this colour change can happen because the chemicals react with food in a person's diet or with medications that a person is taking; this can lead to false test results. Because the faecal immunochemical tests are designed to specifically detect human haemoglobin, they may give more accurate test results than the guaiac-based faecal occult blood tests. The faecal immunochemical tests also target the globin component of haemoglobin, which degrades as it travels through the gastrointestinal tract, and are therefore less likely to detect globin from upper gastrointestinal bleeding. The improved accuracy of faecal immunochemical tests could reduce number of unnecessary referrals for colonoscopy, and reduce the length of time taken for people to be seen by a specialist.

NICE's guidance on suspected cancer includes advice on assessing people presenting to primary care with certain clinical signs and symptoms that may indicate colorectal cancer. It makes the following recommendations:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if:

- they are aged 40 and over with unexplained weight loss and abdominal pain or
- they are aged 50 and over with unexplained rectal bleeding or
- they are aged 60 and over with:
  - iron-deficiency anaemia or
  - changes in their bowel habit, or

- tests show occult blood in their faeces

A suspected cancer referral (for an appointment within 2 weeks) should also be considered for:

- people with a rectal or abdominal mass
- adults aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings:
  - abdominal pain
  - change in bowel habit
  - weight loss
  - iron-deficiency anaemia.

The faecal occult blood tests are recommended to triage referral to secondary care. The tests are intended to be used in selected groups of people who have symptoms that could indicate colorectal cancer, but in whom a definitive diagnosis of cancer is unlikely; that is they have a low probability of having colorectal cancer (their age and symptoms have a positive predictive value within the range of 0.1% to 3% for colorectal cancer). Faecal occult blood tests to assess for colorectal cancer should be offered to adults without rectal bleeding who:

- are aged 50 and over with unexplained:
  - abdominal pain or
  - weight loss, or
- are aged under 60 with:
  - changes in their bowel habit or
  - iron-deficiency anaemia, or
- are aged 60 and over and have anaemia even in the absence of iron deficiency.

Provisional recommendations on the use of these technologies will be formulated by the diagnostics advisory committee at the committee meeting on 19 October 2016.

1.2 Scope of the evaluation

Table 1 scope of the evaluation

Decision question	What is the clinical and cost effectiveness of using quantitative faecal immunochemical tests to triage low risk symptomatic populations for suspected colorectal cancer referrals?
Populations	People presenting to primary care who have symptoms but are considered at low risk of colorectal cancer (that is people for whom faecal occult blood tests are recommended in NICE guideline 12). Where evidence is available subgroups may include : • Age • Sex • People taking medications which increase the risk of gastrointestinal bleeding Faecal haemoglobin levels are thought to differ according to age and sex, and in people taking medications which increase the risk of gastrointestinal bleeding. Different cut-off values may be needed for these subgroups.
Interventions	• HM-JACKarc • FOB Gold • OC Sensor • RIDASCREEN haemoglobin and haemoglobin/haptoglobin
Comparator	1. Guaiac-based faecal occult blood tests 2. Clinical assessment and referral for colonoscopy based on lower gastrointestinal symptoms alone (referral to colonoscopy without triage) The reference standard for assessing the accuracy of both the faecal immunochemical tests and the guaiac based faecal occult blood tests is colonoscopy. People with negative faecal occult blood tests may be followed up in primary care.

Healthcare setting	Primary care
Outcomes	Intermediate measures for consideration may include: • Diagnostic accuracy • Test failure rates • Prognostic implications of false negative results • Uptake of testing by patients • Proportion of people referred to secondary care • Proportion of people followed up in primary care • Number of colonoscopies • Number of colorectal cancer diagnoses • Number of people with advanced adenomas detected and treated • Number of people with other bowel pathologies diagnosed • Time to colonoscopy and diagnosis
	Clinical outcomes for consideration may include: • Morbidity including adverse events associated with colonoscopy • Mortality
	Patient-reported outcomes for consideration may include: • Health related quality of life • Anxiety associated with testing, waiting for results and further diagnostic work up
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Cost of equipment, reagents and consumables • Cost of staff and associated training • Medical costs arising from testing and care including further follow up and safety netting in primary care • Medical costs arising from adverse events which arise from testing or further diagnostic work up, including those associated with false test results and inappropriate treatment.
	The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost

	effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

Further details including descriptions of the interventions, comparators, care pathway and outcomes can be found in the final scope. The performance characteristics of the faecal immunochemical tests are shown below in table 2.

Table 2 performance characteristics of faecal immunochemical tests

Test	Test principle	Sample size	Measuring range	Limit of detection	Limit of quantitation	Diagnostic cut off	Throughput
HM-JACKarc	Immunoturbidimetry	2 mg	7 nanograms/ml to 400 nanograms /ml	0.6 micrograms Hb/g (0.6 nanograms /ml)[a]	1.25 micrograms Hb/g (1.25 nanograms /ml)[a]	10 micrograms Hb/g (10 nanograms /ml)[a]	200 samples per hour
FOB Gold	Immunoturbidimetry	10 mg	Varies according to the analyser used	Varies according to the analyser used	Varies according to the analyser used	To be determined by each laboratory[a]	Dependent on analyser used
OC Sensor assay with PLEDIA and iO analysers	Immunoturbidimetry	10 mg	PLEDIA: 10 nanograms /ml to 1000 nanograms /ml[a] iO: 20 nanograms /ml – 1000 nanograms /ml[a]	PLEDIA: 2 micrograms Hb/g (10 nanograms /ml)[a] iO: 4 micrograms Hb/g (20 nanograms /ml)[a]	PLEDIA: 2 micrograms Hb/g (10 nanograms /ml)[a] iO: 6 micrograms Hb/g (30 nanograms /ml)[a]	10 nanograms /ml[a]	Dependent on analyser used
RIDASCREEN haemoglobin	ELISA	10 mg[a]	Not stated	0.42 micrograms Hb/g	Not stated	2 micrograms Hb/g	Not known
RIDASCREEN haemoglobin/ haptoglobin	ELISA	10 mg[a]	Not stated	0.38 micrograms HbHp/g	Not stated	2 micrograms Hb/g	Not known
[a] information provided by company, not in instructions for use							

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review of the evidence on the clinical effectiveness of the HM-JACKarc, FOB Gold, OC Sensor and RIDASCREEN haemoglobin and haemoglobin/haptoglobin quantitative faecal immunochemical tests. Details of the systematic review can be found starting on page 35 of the diagnostics assessment report.

Studies were included if they reported data for 1 of the technologies in the scope and recruited people with lower abdominal symptoms who were being investigated for possible colorectal cancer. All included studies were appraised using the QUADAS-2 tool if they reported diagnostic accuracy data and the PROBAST checklist if they also reported data for risk-prediction scores. Full details of the critical appraisal can be found starting on page 39 of the diagnostics assessment report.

In total, 10 studies met the inclusion criteria for the systematic review. The studies were reported in 25 published papers and 2 unpublished manuscripts. Additional unpublished data were obtained for 2 of the published studies. Two of the included studies (Krivec et al. 2011; Thomas et al. 2016) were reported as conference abstracts only.

Studies were excluded if they reported a mixed population (screening and symptomatic) and there were no data for the subgroup of patients who were symptomatic. All of the included studies were diagnostic cohort studies; no randomised controlled trials or controlled clinical trials were identified. All 10 included studies were done in Europe, 1 of which was based in England (Thomas et al. 2016) and 3 in Scotland (Godber et al. 2016; McDonald et al. 2013; Mowat et al. 2015). Five of the studies had a [redacted] of bias; 3 because

they excluded participants from the analyses (McDonald et al. 2012; Mowat et al. 2015; Thomas et al. 2016) and 2 because [redacted] (Hospital Clinic de Barcelona 2015; Krivec et al. 2011). [redacted] (Hospital Clinic de Barcelona 2015) [redacted] There were concerns about applicability for all of the included studies because none of them reported data specific to the population included in the scope of the assessment, that is people with symptoms who are judged to be at low risk of colorectal cancer. Only 1 study (Mowat et al. 2015) was carried out in a primary care setting.

The included studies reported data for the HM-JACKarc, FOB Gold and OC Sensor only. No data were found for the RIDASCREEN haemoglobin + haemoglobin/haptoglobin assay. None of the included studies provided comparative accuracy data for the included technologies or made comparisons with guaiac-based faecal occult blood tests.

Diagnostic accuracy

The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to calculate summary sensitivity and specificity estimates and to create HSROC curves for meta-analyses, which included 4 or more studies. For meta-analyses that included less than 4 studies, separate pooled estimates of sensitivity and specificity were calculated using random-effects logistic regression. Data were grouped by assay, target condition and the threshold used to determine a positive test.

OC Sensor

Five studies reported data for the OC Sensor assay. One used the iO analyser (Mowat et al. 2015), 1 used the OC Sensor Diana analyser (McDonald et al. 2013), 2 used the MICRO desktop analyser (Rodriguez-

Alonso et al. 2015; Terhaar sive Droste et al. 2011) and the fifth study did not report the analyser that was used (Cubiella et al. 2014).

Accuracy for colorectal cancer

All 5 studies reported diagnostic accuracy for colorectal cancer, although the prevalence of colorectal cancer ranged from 2.1% to 12.3%. Mowat et al. (2015) was the only study done in a primary care setting. All studies reported the accuracy of a single faecal sample only and used varying thresholds to determine a positive test. A summary of the results is shown in table 3. The full results can be found starting on page 49 of the diagnostics assessment report.

Table 3 Accuracy of the OC Sensor for colorectal cancer

Study	Threshold (micrograms Hb/g faeces)	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable haemoglobin			
Mowat et al. 2015	0	100 (87.7, 100)	43.4 (39.7, 47.1)
Rodríguez-Alonso et al. 2015	0	100 (88.4, 100)	43.3 (40.1, 46.4)
Summary estimate		**100 (93.8, 100)**	**43.3 (40.9, 45.7)**
10 micrograms Hb/g faeces			
McDonald et al. 2012	≥10	100 (54.1, 100)	93.8 (90.3, 96.3)
Mowat et al. 2015	≥10	89.3 (71.8, 97.7)**	79.1 (75.9, 82)
Rodríguez-Alonso et al. 2015	≥10	96.7 (82.8, 99.9)	79.9 (77.2, 82.3)
Terhaar sive Droste 2011	≥10	[redacted]	[redacted]
Summary estimate		**92.1 (86.9, 95.3)**	**85.8 (78.3, 91.0)**
15 micrograms Hb/g faeces or equivalent			
Rodríguez-Alonso et al. 2015	≥15	96.7 (82.8, 99.9)	83.1 (80.6, 85.4)
Terhaar sive Droste 2011	≥15	[redacted]	[redacted]
Summary estimate		**92.3 (86.6, 96.1)**	**86.9 (85.6, 88.1)**
20 micrograms Hb/g faeces or equivalent			
Cubiella et al. 2014	≥20	87.6 (79.0, 93.2)	77.4 (74.0, 80.4)
Rodríguez-Alonso et al 2015	≥20	93.3 (77.9, 99.2)	86.1 (83.8, 88.2)
Terhaar sive Droste 2011	≥20	[redacted]	[redacted]
Summary estimate		**89.5 (84.9, 93.1)**	**86.6 (85.4, 87.7)**
Other thresholds			
Terhaar sive Droste 2011	≥30	[redacted]	[redacted]
Terhaar sive Droste 2011	≥40	[redacted]	[redacted]
Abbreviation: CI, confidence interval.			

The EAG considered that the optimal diagnostic threshold for colorectal cancer was either 10 or 15 micrograms Hb/g faeces, but noted that the most

data were available for 10 micrograms Hb/g faeces. Test accuracy data from Mowat et al. (2015) and Rodriguez-Alonso et al. (2015) were used to illustrate diagnostic outcomes for a hypothetical cohort of 1,000 people, assuming a prevalence of colorectal cancer of 3.3%, and using thresholds of both 10 or more micrograms Hb/g faeces and any detectable haemoglobin (4 or more micrograms Hb/g faeces). The results are shown in table 4.

Table 4 Modelled outcomes for OC Sensor (colorectal cancer)

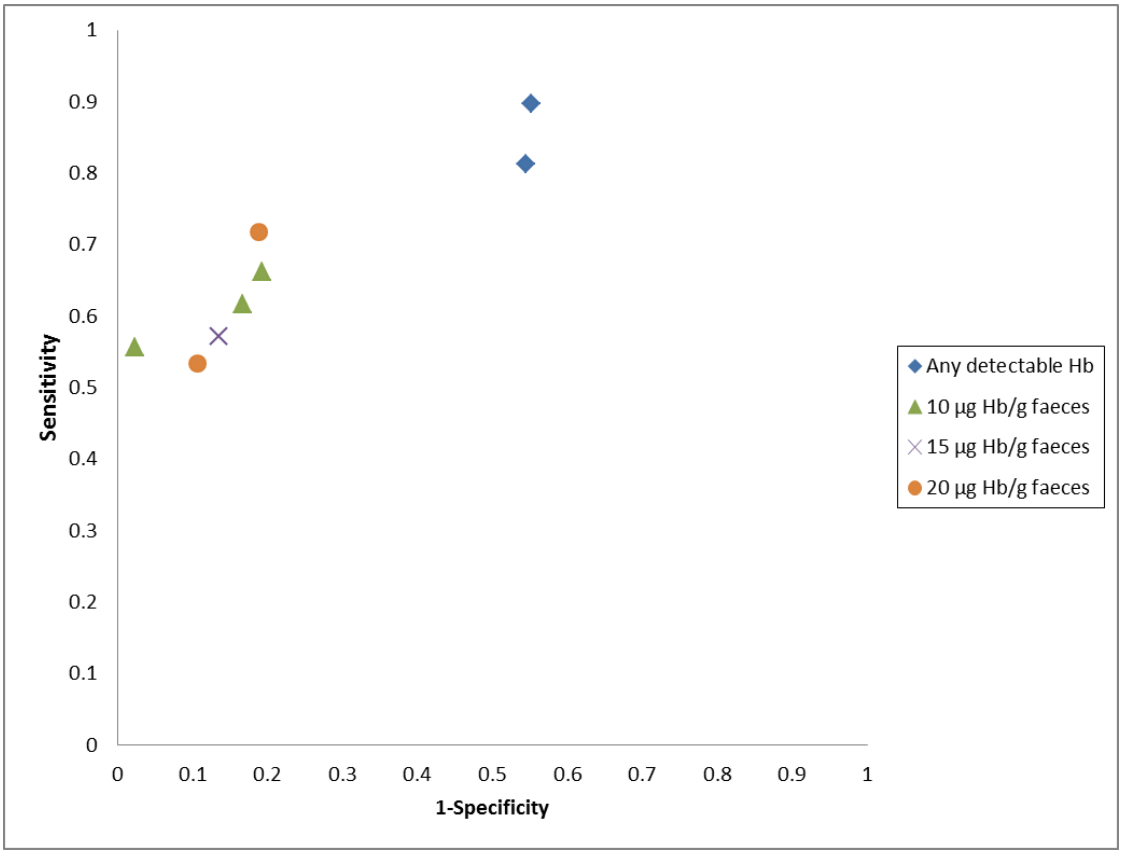
Threshold	10 or more micrograms Hb/g faeces	4 or more micrograms Hb/g faeces
Correct referrals for colonoscopy (true positives)	31	33
Incorrect referrals for colonoscopy (false positives)	198	548
Missed colorectal cancers (false negatives)	2	0
Colonoscopies correctly avoided (true negatives)	769	419

Accuracy for colorectal cancer and high-risk adenomas

Four studies (Cubiella et al. 2014; McDonald et al. 2012; Mowat et al. 2015; Rodriguez-Alonso et al. 2015) reported diagnostic accuracy for advanced neoplasia, which includes both colorectal cancer and high-risk adenoma. The definition of high-risk adenoma and the thresholds used varied between studies. Expanding the target condition reduced the sensitivity of the test. The results of this analysis are summarised below in Figure 1. Full results of this analysis can be found starting on page 56 of the diagnostics assessment report. The EAG noted that although expanding the target condition reduces the sensitivity of the test, these data suggest that the relatively high proportion of false positives seen with faecal immunochemical tests when the target condition is colorectal cancer could be associated with some treatment benefit. This is because the data indicate that substantial numbers of people

who have false positive results for colorectal cancer may be diagnosed with other bowel pathologies and have treatment benefits as a result of referral for colonoscopy after a positive faecal immunochemical test.

Figure 1 ROC space plot for OC sensor for detecting colorectal cancer and high-risk adenomas



Test accuracy data from Mowat et al. (2015) and Rodriguez-Alonso (2015) were used to model outcomes for a hypothetical cohort of 1,000 people assuming a prevalence of colorectal cancer and high-risk adenomas of 11.5%, using thresholds of both 0 or more micrograms Hb/g faeces, and any detectable haemoglobin (4 or more micrograms Hb/g faeces). The results of this are shown below in table 5.

Table 5 Modelled outcomes for OC Sensor (colorectal cancer and high-risk adenomas)

Threshold	10 or more micrograms Hb/g faeces	4 or more micrograms Hb/g faeces
Correct referrals for colonoscopy (true positives)	72	96
Incorrect referrals for colonoscopy (false positives)	157	485
Missed colorectal cancers (false negatives)	2	0
Missed high-risk adenomas (false negatives)	40	18
Colonoscopies correctly avoided (true negatives)	729	401

Accuracy for other target conditions

Three studies reported diagnostic accuracy data for various non-malignant or composite target conditions. McDonald et al. (2012) reported a sensitivity of 57.0% (95% confidence interval [95% CI] 45.8% to 67.6%) and a specificity of 99% (95% CI 96.3% to 99.9%) for all colorectal cancers, high-risk adenomas and inflammatory bowel disease using a threshold of 10 or more micrograms Hb/g faeces. Mowat et al. (2015) used the same threshold and reported a sensitivity of 68.6% (95% CI 58.7% to 77.5%) and a specificity of 83.6% (95% CI 80.6% to 86.4%) for the same composite target condition. Terhaar sive Droste et al. (2011) [redacted]. Full results of this analysis can be found starting on page 60 of the diagnostics assessment report.

HM-JACKarc

Three studies reported accuracy data for the HM-JACKarc automated system (Auge et al. 2016; Godber et al. 2016; Thomas et al. 2016). All 3 studies were done in outpatient clinic settings and used single faecal samples.

Accuracy for colorectal cancer

Two studies (Godber et al. 2016; Thomas et al. 2016) reported accuracy data for colorectal cancer. The prevalence of colorectal cancer was 2.2% in Godber et al. (2016) and 4.9% in Thomas et al. (2016). The results reported by the studies are summarised in table 6. Full results can be found starting on page 69 of the diagnostics assessment report.

Table 6 Accuracy of HM-JACKarc for colorectal cancer

Study	Threshold (micrograms Hb/g faeces)	Sensitivity % (95% CI)	Specificity % (95% CI)
Godber et al. (2016)	≥10	100 (71.5, 100)	76.6 (72.6, 80.3)
Thomas et al. (2016)	≥7	91.3 (72.0, 98.9)	79.2 (75.3, 83)
Abbreviation: CI, confidence interval.			

The EAG considered that a threshold of either 7 or more or 10 or more micrograms Hb/g faeces provided the optimal diagnostic accuracy for colorectal cancer. Test accuracy data from Godber et al. (2016) were used to model outcomes for a hypothetical cohort of 1,000 people, assuming a prevalence of colorectal cancer of 2.2%. The results of this analysis are shown in table 7.

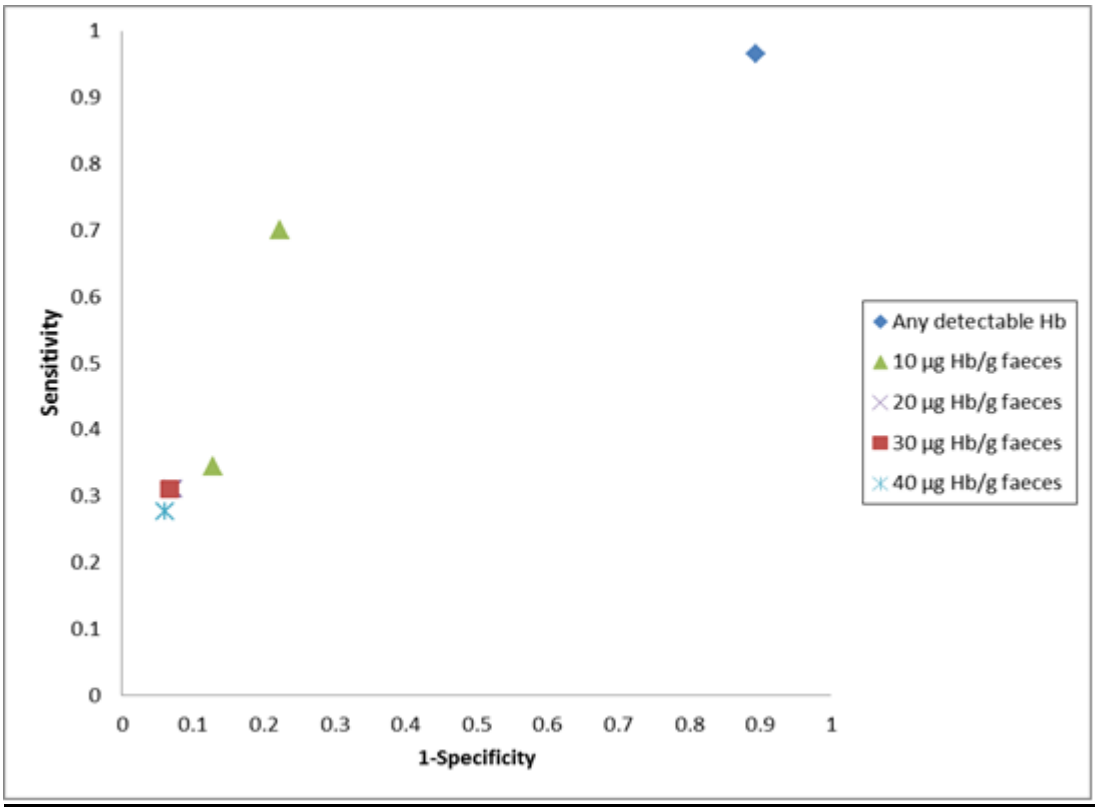
Table 7 Modelled outcomes for HM-JACKarc (colorectal cancer)

Threshold 10 or more micrograms Hb/g faeces	
Correct referrals for colonoscopy (true positives)	22
Incorrect referrals for colonoscopy (false positives)	229
Missed colorectal cancers (false negatives)	0
Colonoscopies correctly avoided (true negatives)	749

Accuracy for colorectal cancer and high-risk adenomas

Two studies (Auge et al. 2016; Godber et al. 2016) reported data for a target condition of colorectal cancer and high-risk adenoma. Each study used a different definition of high-risk adenoma and reported different thresholds. The sensitivity estimates varied widely because of differences in the included populations. The results of the analysis are shown in Figure 2. Full results can be found starting on page 69 of the diagnostics assessment report.

Figure 2 ROC space plot for HM-JACKarc for detecting colorectal cancer and high-risk adenomas



Test accuracy data from Godber et al. (2016) were used to illustrate diagnostic outcomes for a hypothetical cohort of 1,000 people, assuming a prevalence of colorectal cancer and high-risk adenoma of 5.9%, and using a threshold of 10 or more micrograms Hb/g faeces. The results of this analysis are shown in table 8.

Table 8 Modelled outcomes for HM-JACKarc (colorectal cancer and high-risk adenoma)

Threshold ≥10 micrograms Hb/g faeces	
Correct referrals for colonoscopy (true positives)	45
Incorrect referrals for colonoscopy (false positives)	205
Missed colorectal cancers (false negatives)	0
Missed high-risk adenomas (false negatives)	22
Colonoscopies correctly avoided (true negatives)	727

One study (Auge et al. 2016) also investigated the impact of multiple samples and sex on the accuracy of the HM-JACKarc for detecting colorectal cancer and high-risk adenoma. The study had a prevalence of colorectal cancer of less than 1%. The authors reported that 100% sensitivity could be achieved by using a threshold of any detectable haemoglobin and using the highest value reported in 2 consecutive samples, however this reduced the specificity to 3.3%. Data were reported for single or multiple samples using a range of thresholds from any detectable haemoglobin to 40 or more micrograms Hb/g faeces. At thresholds above any detectable haemoglobin, using consecutive samples increased the test's sensitivity but this was still low at under 50% for all estimates. The full details of this analysis can be found starting on page 69 of the diagnostics assessment report.

Auge et al. (2016) also reported that sensitivity estimates at all thresholds were lower when the test was used in women compared with men. Sensitivity estimates ranged from 8.3% at a threshold of 40 or more micrograms Hb/g faeces to 91.7% with any detectable haemoglobin for women, compared with a range of 41.2% at all thresholds above 20 or more micrograms Hb/g faeces to 100% with any detectable haemoglobin for men. Conversely, specificity

estimates tended to be higher in women than in men. Full details of this analysis can be found on page 73 of the diagnostics assessment report.

Accuracy for other target conditions

Two studies (Godber et al. 2016; Thomas et al. 2016) reported accuracy data for various non-malignant and composite target conditions. Godber et al. (2016) defined significant bowel disease as colorectal cancer, higher risk adenoma, inflammatory bowel disease or colitis, and reported sensitivity and specificity estimates of 68.9% and 80.2% respectively at a threshold of 10 micrograms Hb/g faeces. Thomas et al. (2016) defined significant bowel disease as colorectal cancer, high-risk adenoma or inflammatory bowel disease and reported sensitivity and specificity estimates of 72.1% and 80.6% respectively at a threshold of 7 micrograms Hb/g faeces. Godber et al. (2016) also reported data for a range of thresholds between 10 and 40 micrograms Hb/g faeces, which can be found on page 76 of the diagnostics assessment report.

FOB Gold

Two studies reported data for the FOB Gold assay, 1 which was reported in a conference abstract only used the Roche Modular P/917 analyser (Krivec et al. 2011) and 1 which is currently unpublished used the SENTiFIT 270 analyser (Hospital Clinic de Barcelona 2015).

Accuracy for colorectal cancer

Hospital Clinic de Barcelona (2015) assessed the accuracy of FOB Gold for detecting colorectal cancer [redacted]

[redacted]

Table 9 Modelled outcomes for FOB Gold (colorectal cancer)

Threshold 6.8 or more micrograms Hb/g faeces	
Correct referrals for colonoscopy (true positives)	[redacted]
Incorrect referrals for colonoscopy (false positives)	[redacted]
Missed colorectal cancers (false negatives)	[redacted]
Colonoscopies correctly avoided (true negatives)	[redacted]

Accuracy for advanced neoplasia (colorectal cancer or high-risk adenoma)

Hospital clinic de Barcelona reported the accuracy of the FOB Gold for detecting colorectal cancer or high-risk adenoma using a threshold [redacted] The study also investigated the effect of using 2 consecutive samples, full details can be found on page 78 of the diagnostics assessment report.

Accuracy for other target conditions

Krivec et al. (2011) reported a sensitivity of 45.2% and a specificity of 92.3% for significant bowel disease (cancer, polyps or bleeding) using a threshold of 9.35 micrograms Hb/g faeces. Hospital Clinic de Barcelona (2015) reported accuracy data for detecting significant bowel disease [redacted]

[redacted] Full results of the Hospital Clinic de Barcelona (2015) study can be found on page 78 of the diagnostics assessment report.

Evidence on other intermediate outcomes

Test failures

Mowat et al. (2015) reported that less than 1% of samples were considered unsuitable for analysis using the OC Sensor.

Test uptake

Four of the included studies that reported data for the OC Sensor reported test uptake (Cubiella et al. 2014; McDonald et al. 2013; Mowat et al. 2015; Rodriguez-Alonso et al. 2015), which ranged from 41% to 98%. Methods of inviting patients to take a test varied between studies.

Two of the included studies that reported data for the HM-JACKarc reported test uptake. Godber et al. (2016) reported an uptake of 56% when collection devices and information were sent by post whereas Thomas et al. (2016) reported an uptake of 66% when collection devices and uptake were provided at an outpatient appointment.

Management decisions

Mowat et al. (2015) reported that 11% of patients for whom a FIT sample was analysed were not referred for secondary care, 69% were referred for an endoscopy, and 20% were referred to an outpatient clinic. However, decisions about the urgency of the referral were made before using FIT.

Prediction modelling studies

Two studies (Cubiella et al. unpublished; Rodriguez-Alonso et al. 2015) reported data on using prediction models, which included results of faecal immunochemical tests. These studies were also appraised with the PROBAST tool. The studies were classified as having high concerns about the applicability of the included populations, and overall were rated as being at a high risk of bias. Full details of the PROBAST assessment can be found on page 47 of the diagnostics assessment report.

Rodriguez-Alonso et al. (2015) did a multivariate analysis to identify independent predictors of colorectal cancer and advanced neoplasia. Faecal haemoglobin was measured using the OC Sensor assay. The model included age as a categorical variable. The following variables were identified as independent predictors of colorectal cancer:

- male sex (odds ratio [OR] 2.39; 95%CI 1.039 to 5.519; p=0.041)
- iron-deficiency anaemia (OR 2.99; 95% CI 1.27 to 7.03; p=0.012)
- faecal haemoglobin (OR 86.60; 95% CI 11.70 to 64.16; p<0.001).

Full details of this analysis can be found starting on page 61 of the diagnostics assessment report.

A pre-publication copy of a manuscript by Cubiella et al. (2016) reported the development and validation of a risk score known as the FAST score (faecal haemoglobin, age and sex test). Faecal haemoglobin was measured using the OC Sensor, OC–Auto (an earlier version of the OC Sensor) and FOB Gold assays. The logistic regression model included age as a continuous variable, and sex, and faecal haemoglobin as categorical variables. The results of the model suggested that a FAST score of 4.5 or more had a sensitivity of 89.3% (95% CI 84.1% to 93.0%) and a specificity of 82.3% (95% CI 81.1% to 83.5%) for colorectal cancer. To avoid missing any colorectal cancers, a lower FAST score threshold of 2.12 or more was needed which gave a sensitivity of 100% (95% CI 97.7% to 100%) and a specificity of 19.8% (95% CI 18.6% to 21.1%).

Full details of this analysis can be found starting on page 62 of the diagnostics assessment report.

2.2 Costs and cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care. The EAG also constructed a de novo economic model to assess the cost effectiveness of the quantitative faecal immunochemical tests.

Systematic review of cost-effectiveness evidence

The EAG carried out searches to identify published economic evaluations and cost-effectiveness data on using quantitative faecal immunochemical tests in a symptomatic population. Only 1 study was found which reported an economic analysis of using faecal immunochemical tests in symptomatic people; the economic analysis to support the development of recommendations on faecal occult blood tests in NICE's guideline on suspected cancer. Faecal immunochemical tests were included in this analysis in a scenario analysis. Faecal occult blood tests were included in the base case, which indicated that guaiac based faecal occult blood tests and barium enema were cost effective compared with colonoscopy at a maximum acceptable incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained. In a scenario analysis, faecal immunochemical tests dominated (cost less and were more effective than) barium enema and were cost effective at a maximum acceptable ICER of £20,000 per QALY gained. Full details of the review can be found starting on page 82 of the diagnostics assessment report.

Economic analysis

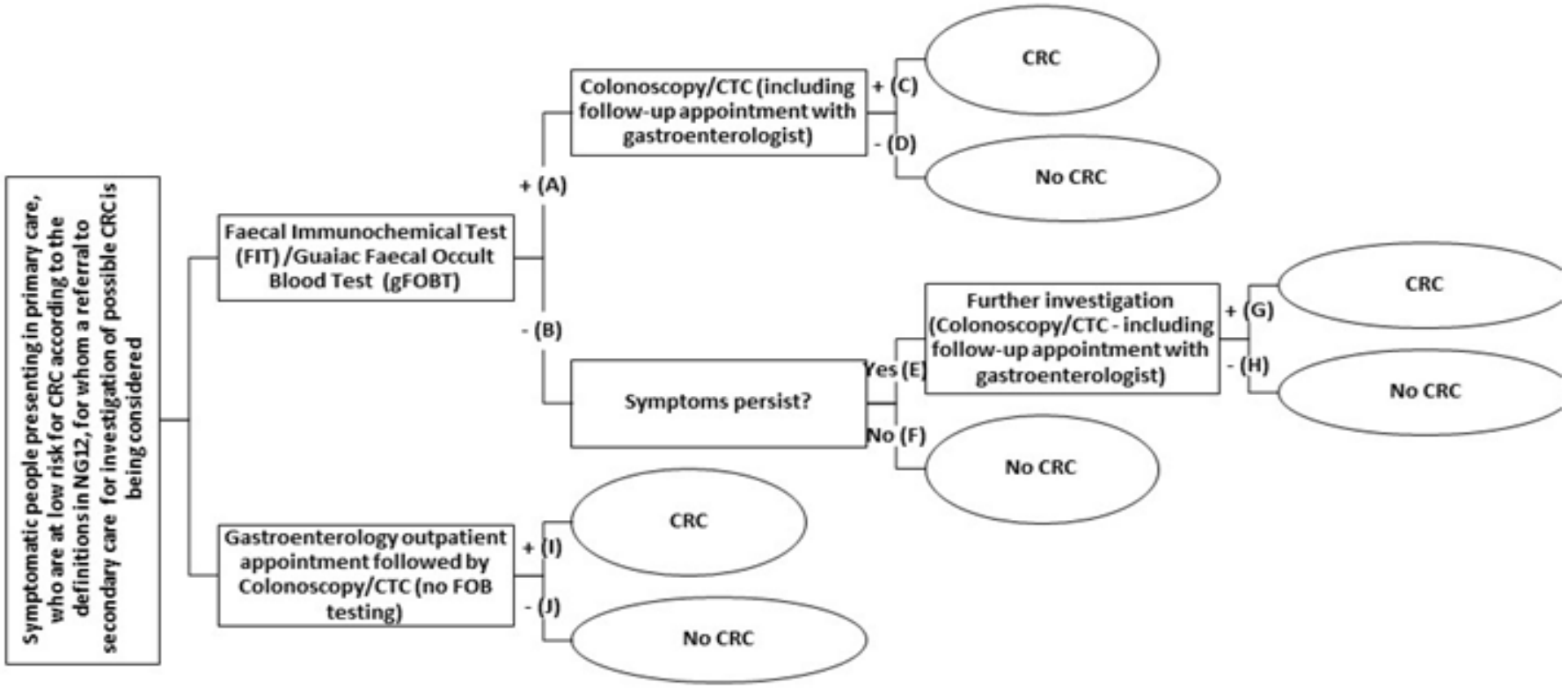
The EAG developed a de novo economic model to explore the cost effectiveness of using a quantitative faecal immunochemical test as a triage step to investigate symptomatic people, with a low risk of colorectal cancer,

presenting to primary care. The model took the perspective of the NHS and personal social services. In the base case, it compared the use of 2 quantitative faecal immunochemical tests, the OC sensor and HM-JACKarc assays, with both guaiac faecal occult blood tests and no triage, that is referral straight to colonoscopy. The FOB Gold assay was not included in the base case because no data were available for the optimal threshold (10 or more micrograms Hb/g faeces) determined by the EAG in the clinical-effectiveness analyses. All costs and effects included in the model were discounted by 3.5%.

Model structure

The model consisted of 3 parts. The first part was a decision tree with a 1-year time horizon, which modelled the results of investigations for colorectal cancer (faecal immunochemical test, guaiac faecal occult blood test or no triage) for a cohort of symptomatic patients presenting to primary care. A positive faecal immunochemical test or guaiac-based faecal occult blood test resulted in referral for colonoscopy and a negative test resulted in a watchful waiting strategy, in which further investigations were done if a person's symptoms persisted. The decision tree was followed by 2 Markov state-transition models. One Markov model had a lifetime time horizon and a 1-year cycle length and was used to estimate costs, life years and QALYs associated with the treatment and progression of colorectal cancer. The initial distribution of patients across the stages of disease at diagnosis was determined using data from the UK's National Cancer Intelligence Network. The other Markov model had a simple alive or dead structure and estimated life years and QALYs for people who did not have colorectal cancer, using UK life tables to model survival. The structure of the decision tree is shown below in Figure 3. Further details of the model structure can be found starting on page 91 of the diagnostics assessment report.

Figure 3 Structure of the decision tree



Model inputs

The model was populated with data from the clinical-effectiveness review, published literature and expert opinion. Full details of the model inputs can be found starting on page 95 of the diagnostics assessment report. Diagnostic-accuracy data were taken from the clinical-effectiveness review. The EAG concluded that a threshold of 10 micrograms Hb/g faeces with a single sample provided the optimal rule-out performance, that is, the threshold gave the maximum sensitivity and specificity, and had the lowest number of colorectal cancers missed. Data at this threshold were available for the HM-JACKarc and OC sensor assays. Data on the accuracy of guaiac-based faecal occult blood tests were taken from Gillberg et al. (2012), which was used in the economic model for NICE's guidance on suspected cancer. The accuracy estimates used are shown in table 10 below. The predictive values were calculated by the EAG assuming a prevalence of colorectal cancer of 1.5% to correspond with the prevalence assumed in NICE's guidance on suspected cancer.

Table 10 Diagnostic accuracy estimates used in the model

Accuracy measure	OC Sensor	HM-JACKarc	Guaiac-based faecal occult blood test
Sensitivity (95% CI)	92.1% (86.9% to 95.3%)	100% (71.5% to 100%)	50% (15.0% to 85.0%)
Specificity (95% CI)	85.8% (78.3% to 91.0%)	76.6% (72.6% to 80.3%)	88% (85.0% to 89.0%)
PPV	8.9%	6.1%	5.7%
NPV	99.8%	100%	99.1%
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.			

Costs

Direct costs included in the model were test costs, cost of colonoscopy or CT colonoscopy, adverse event costs, CT scan costs, costs of first and follow-up investigations, cancer staging and treatment, drug costs, and GP and hospital visits. No costs were included in the Markov model used to model outcomes

for people without colorectal cancer. Costs were obtained from companies, published literature and routine sources of NHS costs. The following test costs were used in the model:

- OC Sensor £4.53 per test
- HM-JACKarc £6.04 per test
- FOB Gold £1.96 per test
- guaiac-based faecal occult blood test £0.78 (rounded to 2 significant figures) per test
- colonoscopy £372 per test
- CT colonography £136 per test
- CT scan £116 per test.

Health-related quality of life and quality-adjusted life-year decrements

No disutilities for bleeding and perforation during colonoscopy were included in the model, because no evidence was found on quality-of-life effects in the literature and the events are often of short duration. The rates of adverse events from colonoscopy were assumed to be 0.26% for bleeding, 0.05% for perforation, and 0.0029% for death. Utilities associated with the different stages of colorectal cancer were taken from Ness et al. (1999) and sex- and age-related utilities for healthy patients were taken from Kind et al. (1999). Further details of the utilities included in the model can be found starting on page 110 of the diagnostics assessment report.

Base-case results

For the purposes of decision-making, the ICERs per QALY gained or lost will be considered. The following key assumptions were applied in the base-case analysis:

- People who had a false negative faecal immunochemical test or guaiac-based faecal occult blood test and whose symptoms persisted were diagnosed within 1 year if they survived.

- The optimal threshold for the interventions was 10 or more micrograms Hb/g faeces.
- People who had a delayed diagnosis had an increased probability of progressing to a more advanced cancer state.
- Costs of laboratory staff were the same for both faecal immunochemical tests and guaiac-based faecal occult blood tests.
- Testing had no long-term (after 1 year) effect on costs or QALYs in people without colorectal cancer.
- Any differences in costs between the tests in patients without colorectal cancer occurred in year 1 only.
- The prevalence of colorectal cancer was 1.5%.
- The probabilities of adverse events during or after colonoscopy were as follows:
  - bleeding 0.26%
  - bowel perforation 0.05%
  - death 0.0029%.
- Only patients with a negative test results whose symptoms did not persist did not have a colonoscopy.
- The cost of a colonoscopy or CT colonography included a follow-up appointment with a gastroenterologist.
- The adverse-event rates associated with CT colonography were the same as for colonoscopy.
- A CT scan was done for all patients with colorectal cancer to stage the disease.
- After year 15 in the colorectal cancer Markov model, colorectal cancer related mortality remains constant, but overall mortality increases because age-specific mortality is included from UK life tables.

The results of the base case are shown below with the fully incremental probabilistic analysis in table 11 and the pairwise comparisons in table 12. The ICERs for the deterministic analysis were slightly higher than those in the

probabilistic analysis. Full results of the base case can be found starting on page 117 of the diagnostics assessment report.

Table 11 base-case results - fully incremental probabilistic analysis

	QALYs	Cost	Incremental QALYs	Incremental cost	ICER
gFOBT	18.6415	£230.49	–	–	–
OC sensor	18.6439	£242.51	0.0024	£12.02	£5,039
No triage	18.6440	£500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6444	£272.50	0.0005	£29.99	£61,619
Abbreviations: gFOBT, guaiac-based faecal occult blood test; QALY, quality-adjusted life year.					

The pairwise results suggest that both the OC sensor and the HM-JACKarc are cost effective compared with both guaiac-based faecal occult blood testing and no triage. The fully incremental probabilistic analysis suggests that the OC sensor assay is cost effective. Despite dominating no triage, when compared with the OC Sensor assay, the HM-JACK has a high ICER because of the very small difference in QALYs and higher cost, which is accounted for by the test having a greater number of positive results and consequently a higher number of colonoscopies.

Table 12 base-case results - pairwise comparisons

Intervention	Comparator	Deterministic			Probabilistic		
		Incremental QALYs	Incremental costs	ICER	Incremental QALYs	Incremental costs	ICER
HM-JACKarc	gFOBT	0.0023	£42.47	£18,296	0.0029	£42.01	£14,626
OC Sensor		0.0020	£12.14	£6,133	0.0024	£12.02	£5,039
HM-JACKarc	No triage	0.0003	−£228.92	Dominates	0.0004	−£228.10	Dominates
OC Sensor		−0.0001	−£259.25	£4,133,559*	−0.0001	−£258.09	£2,578,543[a]
[a] savings per QALY lost							
Abbreviations: gFOBT, guaiac-based faecal occult blood test; QALY, quality-adjusted life year.							

A breakdown of the costs and outcomes in the base case showed that the number of positive tests was highest for the HMJACK-arc (245.36) and lowest for guaiac-based faecal occult blood testing (130.28). OC Sensor had 153.50 positive tests. The increased number of positive tests increases the costs for faecal immunochemical tests because of the associated increase in colonoscopies. No colorectal cancer patients were missed with HM-JACKarc and so no delayed diagnosis occurred with this intervention. By comparison, 92% of colorectal cancers were detected by the OC Sensor and 50% with guaiac-based faecal occult blood tests. Full details of this analysis can be found in Table 48 of the diagnostics assessment report.

The cost-effectiveness acceptability curves for the base case can be found starting on page 124 of the diagnostics assessment report. The curves for all strategies show that at lower maximum acceptable ICERs, the tests associated with the lowest costs have the greatest probability of being cost effective, that is guaiac-based faecal occult blood testing and the OC sensor assay. As the maximum acceptable ICER increases, the HM-JACKarc and guaiac-based faecal occult blood testing have the greatest probability of being cost effective. Pairwise comparisons showed that, when compared with faecal immunochemical testing, no triage would be cost effective only when the maximum acceptable ICER is very high. There was greater uncertainty about which strategy was the most cost effective when the faecal immunochemical tests were compared with guaiac-based faecal occult blood testing.

Analysis of alternative scenarios

The EAG did several scenario analyses to assess the effect of different parameters on the overall results. Full details of the scenario analyses can be found starting on page126 of the diagnostics assessment report.

Test accuracy

The effect of changing assumptions about the accuracy of the tests was explored in several scenario analyses. The changes to the parameters and the effect on the results for 3 scenarios are shown below in table 13.

Table 13 diagnostic accuracy assumptions

Scenario	Threshold FIT	FIT-accuracy estimates (sensitivity, specificity)	gFOBT-accuracy estimates (sensitivity, specificity)	Effect on results
Base case	10 micrograms Hb/g faeces	OC sensor (92.1%, 85.8%) HM-JACKarc (100%, 76.6%)	(50.0%, 88.0%)	–
Accuracy–I	10 micrograms Hb/g faeces	OC sensor (92.1%, 85.8%) HM-JACKarc (100%, 76.6%)	(69.2%, 73.2%)	gFOBT becomes less cost effective
Accuracy–II	10 micrograms Hb/g faeces	OC sensor (92.1%, 85.8%) HM-JACKarc (100%, 76.6%)	(75%, 79.4%)	gFOBT dominated by OC Sensor, HM-JACKarc ICER versus gFOBT £13,482 per QALY gained
Accuracy–III	0 micrograms Hb/g faeces	OC sensor (100%, 43.3%)	(50.0%, 88.0%)	No triage dominated by OC Sensor and OC Sensor ICER versus gFOBT £65,192
Abbreviations: FIT, faecal immunochemical tests; gFOBT, guaiac-based faecal occult blood test; QALY, quality-adjusted life year.				

In a fourth scenario, a threshold of 20 or more micrograms Hb/g faeces was considered, and FOB Gold was included in the analysis using a threshold of 20.5 or more micrograms Hb/g faeces. The deterministic ICERs for this scenario are shown below in table 14.

Table 14 increased threshold (20 or more micrograms Hb/g faeces)

Intervention	Comparator	Incremental QALYs	Incremental cost	ICER
FOB Gold	gFOBT	0.0018	£8.34	£4725
OC Sensor		0.0019	£9.55	£5131
FOB Gold	No triage	−0.0003	−£263.05	£950,152[a]
OC Sensor		−0.0002	−£261.84	£1,449,585.18[a]

[a] money saved per QALY lost

Abbreviations: gFOBT, guaiac-based faecal occult blood tests; QALY, quality-adjusted life year.

In a fifth scenario, the FOB Gold assay was included in the base case, but with a threshold of 6.8 or more micrograms Hb/g faeces, compared with 10 micrograms Hb/g faeces for the HM-JACKarc and OC sensor. The ICER for FOB Gold compared with guaiac-based faecal occult blood testing was £15,720 per QALY gained, and compared with no triage was £2,273,829 saved per QALY lost.

Prevalence of colorectal cancer

Scenario analyses were done in which the prevalence of colorectal cancer was increased from 1.5% in the base case to 3% and 5.4%. Increasing the prevalence reduced the ICERs for the interventions when compared with guaiac-based faecal occult blood testing. However, at 5.4% prevalence the ICER for the OC Sensor when compared with no triage became less cost effective, from £4,133,559 saved per QALY lost to £238,380 saved per QALY lost.

Test costs

A threshold analysis was done, which showed that for the ICER to remain below £30,000 per QALY gained the cost of the HM-JACKarc could be up to £32 more expensive than guaiac-based faecal occult blood tests. The OC Sensor assay could be up to £51 more expensive than guaiac-based faecal occult blood tests.

Initial or delayed diagnosis

In the base case, the following distribution of patients across the Dukes' stages was assumed in the colorectal cancer Markov model:

- stage A 13%
- stage B 37%
- stage C 36%
- stage D 14%.

When it was assumed that there were more patients in stages A and C (16% and 44% respectively) and less patients in stage B (25%) there was a slight loss of QALYs and reduction in costs for all strategies.

When it was assumed that there were more patients in stages A and D (19% and 15% respectively) and less in stages B and C (35% and 32% respectively) there was a slight gain in QALYs and increase in costs for all strategies.

Colorectal cancer mortality and progression

When colorectal cancer progression was not considered in the model, the ICERs reduced from the base-case results for HM-JACKarc and OC Sensor compared with guaiac-based faecal occult blood testing. The ICER for the OC Sensor compared with no triage became less cost effective, £163,305 saved per QALY lost.

Probability of symptoms persisting

When the probability of symptoms persisting after a negative test was doubled from the base case (65%), the interventions remained cost effective despite increased costs from increased colonoscopies and a slight reduction in QALYs. When the probability of symptoms persisting was halved from base case (16.25%), the interventions remained cost effective with a slight QALY increase and reduction in costs compared with the base–case results.

Adverse events for colonoscopy

When a mortality rate of 0.0970% was considered for colonoscopy in a worst case scenario, strategies associated with a higher rate of referrals to colonoscopy (no triage and HM-JACKarc) were dominated by guaiac-based faecal occult blood testing and OC Sensor respectively. When it was assumed that there are no adverse events associated with colonoscopy, no triage was dominated by HM-JACKarc because it provided an equivalent number of QALYs, but cost £227.30 less.

Probability of having CT colonography

When it was assumed that all referrals were to colonoscopy (compared with 88.3% in the base case), with no CT colonography, the cost of each of the testing strategies increased compared with the base case because of the increased cost of colonoscopy.

Probability of having a second index test

When it was assumed that 20% of patients who remained symptomatic after a negative faecal immunochemical test or guaiac-based faecal occult blood test had a second test, the cost of the faecal testing strategies increased, but not enough to affect the overall results.

3 Summary

The results of the clinical-effectiveness review suggest that the HM-JACKarc and OC sensor assays are likely to be accurate enough to rule out colorectal cancer when used as a triage test for people with symptoms of colorectal cancer. The EAG concluded that a threshold of 10 or more micrograms Hb/g faeces provides the best balance between missed colorectal cancers (false negatives) and incorrect referrals to colonoscopy (false positives). Additional clinical analyses suggested that when studies that reported data for colorectal cancer included other bowel pathologies, the number of false positives for colorectal cancer could be partially offset by the detection and treatment of other conditions. Although this is outside of the decision question for

colorectal cancer, data for other colonoscopic findings are often reported by studies on the accuracy of faecal immunochemical tests for colorectal cancer because faecal haemoglobin is a biomarker that is associated with a range of bowel pathologies. The data therefore provide information on additional findings that may occur when faecal immunochemical tests are used for investigating suspected colorectal cancer and to triage referrals.

All data reported used colonoscopy as the reference standard, no comparative data were available to directly compare the faecal immunochemical tests with guaiac-based faecal occult blood tests. There were insufficient data to assess the diagnostic accuracy of the FOB Gold assay at different thresholds and no data were found to assess the accuracy of the RIDASCREEN haemoglobin and haemoglobin/haptoglobin assays.

The base-case results suggest that both the HM-JACKarc and OC Sensor can be considered cost effective when compared with both guaiac-based faecal occult blood testing and no triage. When all interventions and comparators were compared in a fully incremental probabilistic sensitivity analysis, the OC Sensor was the most cost-effective option. The effects of altering key parameters were explored in sensitivity analyses, with the assumptions around the accuracy of guaiac-based faecal occult blood tests and the threshold to determine a positive faecal immunochemical test having the greatest impact on results.

4 Issues for consideration

Clinical effectiveness

The populations included in the studies that met the inclusion criteria for the review were considered to be at a higher risk of colorectal cancer than the population for whom faecal occult blood tests are recommended in NICE's guidance on suspected cancer. That is, patients often had red flag symptoms such as rectal bleeding. The age of the participants also varied between the studies, which affects the likelihood of colorectal cancer being the cause of a

person's symptoms. It is possible that this affects the underlying prevalence of colorectal cancer in the included studies, and so the generalisability of the data to the decision question for this assessment needs to be considered.

The analysis shows that the threshold used to determine a positive result can affect clinical outcomes. The lower the threshold that is used, the lower the risk of missing a colorectal cancer but the number of colonoscopies done increases. The higher the threshold that is used, the higher the risk of missing a colorectal cancer but the number of colonoscopies done decreases. Although the threshold effect limits the amount of data available for pooling, the analysis allows the costs and consequences of using different thresholds to be investigated. The EAG determined that, with the data available, the optimal threshold appears to be 10 or more micrograms Hb/g faeces. Because this is driven by data from populations who are at a slightly higher risk than those in the decision problem, the suitability of the threshold is uncertain.

The target conditions reported in the studies often differed from the target condition in the scope (colorectal cancer). Data have been analysed to take account of this, but it is a source of variability between the studies. The difference in target conditions reported by the studies is a consequence of the test detecting haemoglobin, which is a surrogate marker for colorectal cancer. However, the presence of haemoglobin in faeces may also be caused by other conditions such as polyps or inflammatory bowel disease. When accuracy data for high-risk adenomas were reported by studies, the definitions used to determine high risk varied greatly and this could compound the difficulties in interpreting these data.

Age and sex were included as subgroups in the scope because clinical advice received during scoping suggested that older people may have higher levels of faecal haemoglobin and that men may have higher levels of faecal haemoglobin than women. There were insufficient data for the effect of these 2 variables to be fully explored in subgroup analyses. It is therefore not known

whether age and sex specific thresholds are needed for the faecal immunochemical tests.

No data were available to assess the accuracy of the RIDASCREEN haemoglobin and haemoglobin/haptoglobin assays. The clinical effectiveness of this technology is not known.

No direct comparative data were available to compare the included FIT assays and guaiac-based faecal occult blood tests. Consequently indirect comparisons were made through modelling, using accuracy data from the published literature for the performance of guaiac-based faecal occult blood tests in people who have symptoms of colorectal cancer. Data from the NHS bowel cancer screening programme's faecal immunochemical tests pilot study has shown that faecal immunochemical tests are more accurate than guaiac-based faecal occult blood tests in an asymptomatic population.

Cost effectiveness

The target condition within the decision problem for the assessment is colorectal cancer, however as noted above the tests are designed to detect faecal haemoglobin which is a surrogate biomarker. A positive faecal haemoglobin test may be associated with other conditions, such as inflammatory bowel disease, which benefit from treatment. In the model, patients with these conditions are included as having false positive results; however McDonald et al. (2012) reported accuracy for both colorectal cancer alone, and colorectal cancer, adenomas and inflammatory bowel disease combined for the same cohort and suggested that up to 28.9% of people who had a false positive faecal immunochemical test for colorectal cancer had another bowel pathology. It is therefore possible that some of the patients in the model who are exposed to the adverse events of colonoscopy with no treatment benefit, may benefit from referral in practice.

Sensitivity analyses suggested that the accuracy of guaiac-based faecal occult blood tests affects the results of the model (see page 29). The EAG

tested this assumption because no comparative accuracy data were available to compare faecal immunochemical tests and guaiac-based faecal occult blood tests. The selection of the data source for the accuracy of the guaiac-based faecal occult blood tests, and its applicability to the population outline in the decision problem, is therefore an important consideration. Scenarios which include accuracy estimates from populations considered to be more representative of the population in the decision problem resulted in more favourable ICERs for the faecal immunochemical tests.

The model assumes that all referrals for colonoscopy in the no triage arm are made immediately. Advice from clinical experts during scoping suggested that people who are low risk for colorectal cancer are unlikely to be referred to colonoscopy immediately, with clinical judgement determining who to refer. In some cases this may involve watchful waiting, which has not been modelled because of the absence of data. It is therefore possible that the effectiveness of current practice for referral without faecal haemoglobin triage testing has been overestimated; however because both the HM-JACKarc and OC sensor appear to cost effective in the base case compared with referral straight to colonoscopy this is unlikely to change the overall conclusions.

The model assumes that all the colorectal cancers that are missed by the faecal haemoglobin tests (false negatives) are picked up within 12 months. This assumption is in line with both the assumptions made in the model used for NICE's guidance on suspected cancer, and the recommendation made in the guidance on clinical safety netting for people with negative test results. However, it is not certain whether detection within 12 months is achieved in practice.

The model does not include disutility for adverse events associated with colonoscopy such as bleeding or perforation. Although bleeding is likely to resolve quickly and not have a substantial effect on quality of life, bowel perforation could be associated with clinical sequelae that have a significant effect, for example abdominal infection. It is therefore possible that triage

strategies that send more people to colonoscopy are less cost effective than the analyses suggest.

Although detecting high-risk adenomas is outside of the scope of the current decision problem, which focuses on colorectal cancer, they can be a cause of positive faecal haemoglobin tests. Consequently, the rate of incidental detection of high-risk adenomas was reported by several of the included studies. The accuracy data shows that if the threshold is set to 10 or more micrograms Hb/g faeces, then 22 to 40 people with high-risk adenomas would be missed by the faecal immunochemical tests. If the threshold is set lower to any detectable haemoglobin, a greater number of high-risk adenomas would be identified but there would be an increase of around 300 people being sent for an unnecessary colonoscopy, which has associated risks and inconvenience for people. It is also not clear how many high-risk adenomas would be missed by current practice or guaiac-based faecal occult blood testing to provide a comparison with the number missed by the faecal immunochemical tests.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

People with cancer are protected under the Equality Act 2010 from the point of diagnosis.

Faecal haemoglobin concentrations may be greater in men than women, and may also increase with age. Test cut-offs may therefore vary according to age and sex (Fraser 2012).

The tests may not be suitable for use in people with an existing diagnosis of inflammatory bowel disease, some of whom may be covered by the disability provision of the Equality Act 2010. Disabled people may need support to

obtain and submit a stool sample, and to understand the purpose of the test and the implications of the test results.

Cultural preferences may influence the acceptability of tests that need a stool sample to be collected.

6 Implementation

There will need to be agreement between primary care, gastric surgery, gastroenterology and laboratories about suitable local pathways, as well as training on using these pathways, to support adoption of faecal immunochemical tests and appropriate care for patients. Information for patients may also have to be developed to explain both the purpose of the test and the most effective way to collect a sample.

Laboratories reporting faecal immunochemical tests will need to take part in recognised quality assurance schemes.

7 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Kleijnen Systematic Reviews Ltd:

Westwood M, Corro Ramos I, Lang S et al. Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and economic analysis. August 2016.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- Alpha Laboratories
- MAST Group Ltd
- R-Biopharm Rhone Ltd
- Sysmex UK Ltd

Other commercial organisations:

- BIOHIT Healthcare Ltd
- DiaSorin Ltd
- Origin Sciences Ltd

Professional groups and patient/carer groups:

- Beating Bowel Cancer
- Bowel Cancer UK
- Institute of Biomedical Science
- Royal College of Pathologists
- Royal College of Physicians

- Royal College of Nursing

Research groups:

- Cancer Research UK

Associated guideline groups:

None

Others:

- Birmingham Quality (UK NEQAS)
- BIVDA
- Department of Health
- Healthcare Improvement Scotland
- NHS England
- MHRA
- UK National Screening Committee
- Welsh Government

Appendix B: Glossary of terms

Colonoscopy

An investigation that allows doctors to examine the lining of the colon (large intestine) using a flexible tube that contains a camera and light source (colonoscope).

Faecal immunochemical test

A test which detects faecal occult blood using antibodies against human haemoglobin.

Flexible sigmoidoscopy

An investigation that allows doctors to examine the lining of the lower section of the colon (sigmoid) using a flexible tube that contains a camera and light source (sigmoidoscope).

Guaiac faecal occult blood test

A test which detects faecal occult blood using a test device containing guaiac paper. Hydrogen peroxide developer is added to the guaiac paper which reacts with the alpha-guaiaconic acid on the paper creating a blue colour change. Where haemoglobin is present in the sample, the haem speeds up the reaction creating a rapid colour change.

Haemoglobin

A protein molecule found in red blood cells. Its presence in faecal samples indicates that gastrointestinal bleeding may be occurring.

Haptoglobin

A protein which binds to haemoglobin making it less susceptible to breaking down as it passes through the gastrointestinal tract.