

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care

The National Institute for Health and Care Excellence (NICE) is producing guidance on using quantitative faecal immunochemical tests in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the [evidence base](#) (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on quantitative faecal immunochemical tests. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the [Diagnostics Assessment Programme manual](#).

Key dates:

Closing date for comments: 8 December 2016

Second diagnostics advisory committee meeting: 17 January 2017

1 Draft recommendations

1.1 The OC Sensor, HM-JACKarc and FOB Gold quantitative faecal immunochemical tests are recommended for routine adoption in primary care to guide referral for suspected colorectal cancer in people who have symptoms but are at low risk.

The tests should be used in combination with clinical judgement and other test results to decide whether to make a referral using a suspected colorectal cancer pathway for an appointment within 2 weeks or a routine outpatient referral to a specialist.

1.2 Results should be reported using a threshold of 10 micrograms of haemoglobin per gram of faeces. Laboratories adopting the tests should take note of the instructions for use and ask the companies for advice about the performance characteristics when needed.

1.3 There is currently insufficient evidence to recommend the routine adoption of the RIDASCREEN haemoglobin or the RIDASCREEN

haemoglobin/haptoglobin assay in primary care to guide referrals for suspected colorectal cancer in people, who have symptoms but are at low risk.

2 Clinical need and practice

The problem addressed

- 2.1 The purpose of this assessment was to evaluate the clinical and cost effectiveness of using quantitative faecal immunochemical tests in primary care to triage low-risk symptomatic populations (that is, identify those at greatest risk) for suspected colorectal cancer referrals.
- 2.2 Several lower gastrointestinal 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 whether they should be referred for further investigations. The low-risk symptomatic population for whom faecal occult blood testing is recommended is outlined in the NICE guideline on [suspected cancer](#), and is described in further detail below.
- 2.3 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 medicine 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 guaiac-based tests. The faecal immunochemical tests target the globin component of haemoglobin, which degrades as it travels through the gastrointestinal tract, so these tests are less likely to detect globin from upper gastrointestinal bleeding. The improved accuracy of faecal immunochemical tests could reduce the number of unnecessary referrals for colonoscopy, and reduce the length of time taken for people to be seen by a specialist.

The condition

2.4 Colorectal cancer is one of the most common cancers. In 2013 in the UK, 41,112 people were diagnosed with colorectal cancer and 15,903 people died from it (Cancer Research UK, 2016). Risk factors include older age, a family history of the disease, and having familial adenomatous polyposis or Lynch syndrome, colorectal polyps, or ulcerative colitis or Crohn's disease. In addition, Jewish people of central and eastern European family origin are thought to be at increased risk.

The diagnostics and care pathways

Diagnosis

2.5 The NICE guideline 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 or over with unexplained weight loss and abdominal pain or
- they are aged 50 or over with unexplained rectal bleeding or
- they are aged 60 or 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.

2.6 The NICE guideline on suspected cancer also recommends that faecal occult blood tests should be offered to adults without rectal bleeding who:

- are aged 50 or 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 or over and have anaemia without iron deficiency.

2.7 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 of between 0.1% and 3% for colorectal cancer).

- 2.8 If a faecal occult blood test is positive, the NICE guideline on suspected cancer states that people in England should be referred using a suspected cancer referral to establish a diagnosis. Faecal occult blood can be caused by conditions other than colorectal cancer, such as colorectal polyps and inflammatory bowel disease, so further assessment with a colonoscopy is needed to diagnose colorectal cancer; a positive faecal occult blood test should not be used alone.
- 2.9 Colonoscopy is considered to be the gold standard for diagnosing colorectal cancer because the entire colon can usually be seen and biopsies can be taken to assess the tissue in a laboratory to determine whether the sample contains benign or malignant cells. CT colonography can be offered as an alternative for people with comorbidities that make colonoscopy unsuitable. Colonoscopy is usually done as an outpatient procedure, with people having the procedure being offered sedation or painkillers.
- 2.10 The most common finding during a colonoscopy is colorectal polyps, which can be removed using cauterisation or a snare. If colorectal cancer is confirmed, the NICE guideline on [colorectal cancer](#) recommends further imaging tests, such as CT or MRI, to stage the cancer and determine what treatment is needed. Colonoscopy may also find other bowel diseases such as Crohn's disease, ulcerative colitis and diverticulosis, which may need further treatment and follow-up. People with a positive faecal occult blood test but no abnormalities detected during colonoscopy may be referred for further testing if a clinician thinks this is needed.

Treatment

- 2.11 After diagnosis and staging, colorectal cancer may be treated with surgery, chemotherapy and radiotherapy, or sometimes with biological agents such as cetuximab. Treatment depends on the stage of the cancer and is described in more detail in the NICE guideline on diagnosing and managing colorectal cancer.

3 The diagnostic tests

The assessment compared 4 intervention tests with 2 comparators.

The interventions

OC Sensor test

- 3.1 The OC Sensor (Eiken Chemical/MAST Diagnostics) is a quantitative faecal immunochemical test. It comprises faecal sample collection tubes, latex reagent and buffer. The OC Sensor faecal sample collection tubes can hold 10 mg of faeces (Carroll et al. 2014) in 2 ml of buffer. The OC Sensor latex reagent contains latex particles coated with polyclonal antibodies for human haemoglobin. The antibodies bind with haemoglobin present in the faecal sample creating complexes that are detected using turbidimetry.
- 3.2 The test can be run on either the OC Sensor PLEDIA or the OC Sensor iO analyser. The OC Sensor PLEDIA can process up to 320 samples per hour, with a capacity of 200 samples per run. The OC Sensor iO can process up to 88 samples per hour with a maximum capacity of 20 samples per run. The performance of the assay varies according the analyser used. The company states that a cut-off of 10 micrograms Hb/g faeces (50 nanograms/ml) should be used for a symptomatic population.

HM-JACKarc system

3.3 The HM-JACKarc system (Kyowa Medex/Alpha Laboratories) is a fully automated quantitative faecal immunochemical test system. It comprises faecal sample tubes, which incorporate a sample collection device (the Extel Hemo-auto MC A device) and can hold 2 mg of faeces (Carroll et al. 2014) in 2 ml of buffer, and latex agglutination reagent (Extel Hemo-Auto HS) and buffer (Extel Hemo-auto). The reagent contains latex particles that are coated in antibodies specific to human haemoglobin. The antibodies bind to haemoglobin present in the faecal sample creating complexes that are detected using turbidimetry. The assay is compatible with the HM-JACKarc analyser, which reports results as nanograms/ml. The user needs to convert the results to micrograms of haemoglobin (Hb)/g. However, because the test uses 2 mg of sample and 2 ml of buffer, results reported as nanograms/ml convert directly to micrograms of Hb/g faeces, that is 10 nanograms/ml equals 10 micrograms Hb/g faeces. The company suggests a cut-off of 10 micrograms Hb/g faeces for symptomatic populations. The HM-JACKarc analyser can process up to 200 samples per hour, with a maximum capacity of 80 samples per run.

FOB Gold system

3.4 The FOB Gold system (Sentinel/Sysmex) is an automated quantitative faecal immunochemical test system. It comprises faecal sample collection tubes (the Sentifit pierce tube faecal collection device), which collect 10 mg of faeces (Carroll et al. 2014) in 1.7 ml of buffer, and latex agglutination reagent. The FOB Gold latex agglutination reagent contains polyclonal antibodies specific to human haemoglobin, which bind to haemoglobin present in the sample creating complexes that are detected using turbidimetry. The FOB Gold kit has CE-marked applications for a range of clinical chemistry analysers, including

the BioMajesty JCA-6010/C, the SENTiFIT270 and those supplied by Siemens, Beckman Coulter and Abbott. The performance characteristics of the assay vary depending on which analyser is used. The company suggests that each laboratory should establish their own test cut-off according to the population the laboratory serves. The throughput of the test depends on the clinical chemistry analyser used to process the samples.

RIDASCREEN haemoglobin and haemoglobin/haptoglobin assay

3.5 The RIDASCREEN haemoglobin test (R-Biopharm Rhone) is an enzyme immunoassay (ELISA) for the quantitative determination of human haemoglobin in stool samples. The test is run on a microtitre plate using wells coated with polyclonal antibodies for human haemoglobin. The contents of each kit are enough for 96 tests. The instructions for the test suggest that it can be used with laboratory equipment other than the DSX automated ELISA system.

3.6 The test process incorporates 3 incubations and 2 wash steps. During the first incubation, any human haemoglobin present in the sample is captured by the polyclonal antibodies in the sample well. Unbound antigens are removed in the first wash step. Then peroxidase labelled monoclonal antibodies for human haemoglobin (conjugate) are added, which bind to the captured haemoglobin during the second incubation. In the final incubation, hydrogen peroxide and TMB (substrate) is added, which react with the peroxidase creating a colour change that is detected by a plate reader. The values from the plate reader are interpreted by the RIDA-SOFT Win.net software, which reports results as the concentration of haemoglobin per gram of stool (micrograms Hb/g faeces). The company states that 91 tests can be processed manually in 150 minutes, or 546 tests in 7 hours using an automated system. The company recommends a cut-off value of

more than 2 micrograms Hb/g faeces to determine a positive sample.

- 3.7 The company also produces the RIDASCREEN haemoglobin/haptoglobin enzyme immunoassay that can be run in combination with the haemoglobin assay, using the same sample and processing on the same microtitre plate but with the addition of a well coated with polyclonal antibodies for human haptoglobin. Haptoglobin is a protein produced by the liver that binds to haemoglobin, making it less likely to break down as it moves through the gastrointestinal tract. The detection of haptoglobin is claimed to increase the likelihood of detecting lesions in the ascending and transverse colon. The company recommends a cut-off value of 2 micrograms Hb/g faeces to determine a positive test using the haemoglobin/haptoglobin assay.

The comparators

- 3.8 The first comparator used in this assessment is guaiac-based faecal occult blood testing. Guaiac-based tests detect the pseudoperoxidase activity of the haem component of haemoglobin in stool samples using guaiac-test paper and hydrogen peroxide developer. Unlike faecal immunochemical tests, they are not specific to human haemoglobin.
- 3.9 The second comparator is clinical assessment and referral for colonoscopy based on lower gastrointestinal symptoms alone.

4 Evidence

The diagnostics advisory committee ([section 9](#)) considered evidence on quantitative faecal immunochemical tests to assess people presenting to primary care who have symptoms but are at a low risk of colorectal cancer, from several sources ([section 10](#)). Full details of all the evidence are in the [committee papers](#).

Clinical effectiveness

- 4.1 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 included if they reported data for 1 of the intervention 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.
- 4.2 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 high risk of bias. 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 primary care.
- 4.3 The included studies reported data for the HM-JACKarc, FOB Gold and OC Sensor assays only. No data were found for the RIDASCREEN haemoglobin or the RIDASCREEN 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

4.4 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 fewer 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 test

4.5 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 which analyser was used (Cubiella et al. 2014). 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 primary care. 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 1. Additional data from Terhaar sive Droste et al. (2011) were unpublished at the time of writing and cannot be reported here.

Table 1 Accuracy of the OC Sensor for colorectal cancer

Study	Threshold (micrograms Hb/g faeces)	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable haemoglobin: 2 studies			
Mowat et al. 2015	0	100 (87.7, 100)	43.4 (39.7, 47.1)
Rodriguez-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: 4 studies (1 unpublished)			
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)
Rodriguez-Alonso et al. 2015	≥10	96.7 (82.8, 99.9)	79.9 (77.2, 82.3)
Summary estimate		92.1 (86.9, 95.3)	85.8 (78.3, 91.0)
15 micrograms Hb/g faeces or equivalent: 2 studies (1 unpublished)			
Rodriguez-Alonso et al. 2015	≥15	96.7 (82.8, 99.9)	83.1 (80.6, 85.4)
Summary estimate		92.3 (86.6, 96.1)	86.9 (85.6, 88.1)
20 micrograms Hb/g faeces or equivalent: 3 studies (1 unpublished)			
Cubiella et al. 2014	≥20	87.6 (79.0, 93.2)	77.4 (74.0, 80.4)
Rodriguez-Alonso et al 2015	≥20	93.3 (77.9, 99.2)	86.1 (83.8, 88.2)
Summary estimate		89.5 (84.9, 93.1)	86.6 (85.4, 87.7)
Abbreviations: CI, confidence interval; Hb, haemoglobin.			

4.6 The external assessment group (EAG) considered that the optimal diagnostic threshold for colorectal cancer was either 10 or 15 micrograms Hb/g faeces, but noted that 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 micrograms Hb/g faeces and any detectable haemoglobin (4 micrograms Hb/g faeces). The results are shown in table 2.

Table 2 Modelled outcomes for the OC Sensor test (colorectal cancer)

Threshold	10 micrograms Hb/g faeces	4 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
Abbreviation: Hb, haemoglobin.		

4.7 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, with summary sensitivity estimates of 62.9% (95% confidence interval [CI] 55.9% to 69.4%) at a threshold of 10 micrograms Hb/g, 63.9% (95% CI 58.2% to 69.2%) at a threshold of 20 micrograms Hb/g and 84.1% (95% CI 78.3% to 88.8%) at a threshold of any detectable haemoglobin. The sensitivity of the test was lower when the target condition was expanded to include other bowel pathologies. But data from studies that reported results for both colorectal cancer and high-risk adenoma suggested that many false-positive results for colorectal cancer could be from other bowel pathologies that may benefit from treatment.

4.8 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% 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 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. Additional data from Terhaar sive Droste et al. (2011) were unpublished at the time of writing so cannot be reported here.

HM-JACKarc system

- 4.9 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 clinics and used single faecal samples.
- 4.10 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. and 4.9% in Thomas et al. Godber et al. reported a sensitivity of 100% (95% CI 71.5% to 100%) and a specificity of 76.6% (95% CI 72.6% to 80.3%) at a threshold of 10 micrograms Hb/g faeces. Thomas et al. reported a sensitivity of 91.3% (95% CI 72.0% to 98.9%) and a specificity of 79.2% (95% CI 75.3% to 83.0%) at a threshold of 7 micrograms Hb/g faeces. Test accuracy data from Godber et al. 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 3.

Table 3 Modelled outcomes for the HM-JACKarc assay (colorectal cancer)

Threshold of 10 micrograms of haemoglobin/g of 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

- 4.11 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. Godber et al. reported a sensitivity of 70.0% (95% CI 50.6% to 85.3%) and a specificity of 77.8% (95% CI 73.8% to 81.4%) at a threshold of 10 micrograms Hb/g faeces. Auge et al. reported a range of accuracy estimates with sensitivity ranging from 27.6% (95% CI 14.7% to 45.7%) at a threshold of 40 micrograms Hb/g faeces to 96.6% (95% CI 82.8% to 93.4%) at a threshold of any detectable haemoglobin. Specificity ranged from 10.6% (95% CI 6.9% to 15.9%) at a threshold of any detectable haemoglobin to 93.9% (95% CI 89.4% to 96.6%) at a threshold of 40 micrograms Hb/g faeces.
- 4.12 One study (Auge et al. 2016) also investigated the effect of multiple samples and sex on the accuracy of the HM-JACKarc assay 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, but 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 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.
- 4.13 Auge et al. (2016) also reported that sensitivity estimates at all thresholds were lower when the test was used in women than when used in men. Sensitivity estimates ranged from 8.3% at a threshold

of 40 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 micrograms Hb/g faeces to 100% with any detectable haemoglobin for men. Conversely, specificity estimates tended to be higher in women than in men.

- 4.14 Two studies (Godber et al. 2016; Thomas et al. 2016) reported accuracy data for various non-malignant and composite target conditions. Godber et al. defined significant bowel disease as colorectal cancer, higher-risk adenoma, inflammatory bowel disease or colitis. It reported sensitivity and specificity estimates of 68.9% and 80.2% respectively at a threshold of 10 micrograms Hb/g faeces. Thomas et al. defined significant bowel disease as colorectal cancer, high-risk adenoma or inflammatory bowel disease. They reported sensitivity and specificity estimates of 72.1% and 80.6% respectively at a threshold of 7 micrograms Hb/g faeces.

FOB Gold assay

- 4.15 Two studies reported data for the FOB Gold assay. One was reported in a conference abstract only and used the Roche Modular P/917 analyser (Krivec et al. 2011). The other was unpublished at the time of writing and used the SENTiFIT270 analyser (Hospital Clinic de Barcelona 2015). Further data from Hospital Clinic de Barcelona are unpublished and cannot be reported here. 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.

Test failures

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

Test uptake

- 4.17 Four of the included studies reporting 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.
- 4.18 Two of the included studies reporting 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 information were provided at an outpatient appointment.

Management decisions

- 4.19 Mowat et al. (2015) reported that 11% of patients for whom a faecal immunochemical test sample was analysed were not referred to 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 the test.

Prediction modelling studies

- 4.20 Two studies (Cubiella et al. 2016; 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.
- 4.21 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).

4.22 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 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 was needed. This gave a sensitivity of 100% (95% CI 97.7% to 100%) and a specificity of 19.8% (95% CI 18.6% to 21.1%).

Cost effectiveness

Review of economic evidence

4.23 Only 1 study was found that reported an economic analysis of using faecal immunochemical tests in people with symptoms; the economic analysis of faecal occult blood tests in NICE's guideline on [suspected cancer](#). Faecal immunochemical tests were included in a scenario analysis in the guideline. Faecal occult blood tests were included in the base case, which indicated that guaiac-based 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 the scenario analysis, faecal immunochemical tests dominated (cost less and were more effective) barium enema and were cost effective at a maximum acceptable ICER of £20,000 per QALY gained.

Modelling approach

4.24 The EAG developed a de novo economic model to explore the cost effectiveness of using a quantitative faecal immunochemical test to guide referral of people who present to primary care with symptoms but have a low risk of colorectal cancer. 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-based 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 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

4.25 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-based faecal occult blood test or no triage) for a cohort of patients, with symptoms, 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 watchful waiting, 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.

Model inputs

4.26 The model was populated with data from the clinical-effectiveness review, published literature and expert opinion. 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 guideline on [suspected cancer](#). The accuracy estimates used are shown in table 4. 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 guideline on suspected cancer.

Table 4 Diagnostic accuracy estimates used in the model

Accuracy measure	OC Sensor assay	HM-JACKarc assay	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%)
Positive predictive value	8.9%	6.1%	5.7%
Negative predictive value	99.8%	100%	99.1%
Abbreviation: CI, confidence interval.			

Costs

4.27 Direct costs included in the model were test costs, cost of colonoscopy or CT colonography, 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 for outcomes for people without colorectal cancer. Costs were obtained from companies, published literature and routine sources of NHS costs. Test costs were calculated as average costs per test. The following test costs were used in the model:

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

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

4.28 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).

Base-case results

4.29 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 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 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.

4.30 The results of the base case are shown with the fully incremental probabilistic analysis in table 5 and the probabilistic pairwise comparisons in table 6. The ICERs for the deterministic analysis were slightly higher than those in the probabilistic analysis.

Table 5 base-case results - fully incremental probabilistic analysis

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

Table 6 base-case results – probabilistic pairwise comparisons

Intervention	Comparator	Incremental QALYs	Incremental costs	ICER
HM-JACKarc assay	gFOBT	0.0029	£42.01	£14,626
OC Sensor assay		0.0024	£12.02	£5,039
HM-JACKarc assay	No triage	0.0004	-£228.10	Dominates
OC Sensor assay		-0.0001	-£258.09	£2,578,543 ^a
^a savings per QALY lost				
Abbreviations: gFOBT, guaiac-based faecal occult blood test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.				

4.31 The pairwise results suggest that both the OC Sensor and the HM-JACKarc assays 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, the HM-JACKarc assay 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.

4.32 A breakdown of the costs and outcomes in the base case showed that the number of positive tests was highest for the HMJACK-arc assay (245.36) and lowest for guaiac-based faecal occult blood testing (130.28). The OC Sensor assay 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 the HM-JACKarc assay and so no delayed diagnosis occurred with this test. By comparison, 92% of colorectal cancers were detected by

the OC Sensor assay and 50% with guaiac-based faecal occult blood tests.

- 4.33 The cost-effectiveness acceptability 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 assay 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 results

Test accuracy

- 4.34 The effect of changing assumptions about the accuracy of the tests was explored in several scenario analyses. Using alternative sources of accuracy data for guaiac-based faecal occult blood tests did not substantially alter the conclusions. The faecal immunochemical tests remained cost effective compared with guaiac-based faecal occult blood tests.
- 4.35 When a threshold of any detectable haemoglobin was considered for the OC Sensor test it resulted in an increased number of colonoscopy referrals and an ICER of £65,192 compared with guaiac-based faecal occult blood tests.
- 4.36 When a threshold of 20 micrograms Hb/g faeces was considered, and the FOB Gold assay was included in the analysis using a

threshold of 20.5 micrograms Hb/g faeces, this resulted in an ICER of £4,725 per QALY gained for the FOB Gold assay compared with guaiac-based faecal occult blood tests. When compared with no triage, £950,152 was saved per QALY lost.

- 4.37 The FOB Gold assay was included in a scenario analysis with the base-case settings, but with a threshold of 6.8 micrograms Hb/g faeces, compared with 10 micrograms Hb/g faeces for the HM-JACKarc and OC Sensor assays. The ICER for the 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

- 4.38 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 compared with guaiac-based faecal occult blood testing. However, at 5.4% prevalence the ICER for the OC Sensor test 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

- 4.39 A threshold analysis showed that for the ICER to remain below £30,000 per QALY gained the cost of the HM-JACKarc test 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

- 4.40 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%.

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

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

Colorectal cancer mortality and progression

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

Probability of symptoms persisting

4.44 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 the base case (16.25%), the interventions remained cost effective with a slight QALY increase and reduction in costs.

Adverse events for colonoscopy

4.45 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 assay) were dominated by guaiac-based faecal occult blood testing and the OC Sensor test respectively. When it was assumed that there are no adverse events associated with colonoscopy, no triage was dominated by the HM-JACKarc assay because it provided an equivalent number of QALYs, but cost £227.30 less.

Probability of having CT colonography

4.46 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

4.47 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

5 Committee discussion

5.1 The committee discussed the current standard of care for people who present to their GP with symptoms, but who are at a low risk of having colorectal cancer. It noted that recommendations had been made for using faecal occult blood tests to triage referral for this group of people in NICE's guideline on [suspected cancer](#), but heard from clinical specialists that this had not yet been widely adopted in primary care. It heard that people are typically assessed by taking into account their clinical history, their current symptoms and the results of any available tests to establish whether there is a

clinical suspicion of colorectal cancer. If clinical suspicion is sufficiently raised, referral using a suspected cancer pathway for an appointment within 2 weeks is appropriate. The committee noted that in practice clinical history and current symptoms of people in this low-risk group were likely to be heterogeneous, and so management was likely to vary between individual patients and GPs. The committee concluded that it was unlikely that a single current standard of care could be defined for this group because of the complexity of managing and investigating non-specific symptoms in practice.

- 5.2 The committee discussed the potential benefits that may be associated with using faecal immunochemical tests in primary care. It heard from clinical specialists that faecal immunochemical tests are thought to be more accurate than guaiac-based faecal occult blood tests because they use immunochemical detection methods that are specific to human haemoglobin. They are also suitable for use with automated analysers, which allow high-throughput batch testing. It also heard from a patient specialist that faecal immunochemical tests often had sample collection devices that are easier to use than guaiac-based faecal occult blood tests and they need fewer samples, which makes them more acceptable to people and so may increase test uptake. The committee concluded that faecal immunochemical tests may have substantial analytical and practical advantages over guaiac-based faecal occult blood tests.

Clinical effectiveness

- 5.3 The committee discussed the evidence base for the clinical effectiveness of the quantitative faecal immunochemical tests for triaging people with symptoms who are at a low risk of colorectal cancer. It noted that there were 10 included studies that reported data for the OC sensor, HM-JACKarc and FOB Gold assays. It also noted that none of the included studies reported data for the

RIDASCREEN haemoglobin or the RIDASCREEN haemoglobin/haptoglobin assays. It therefore concluded that, in the absence of any data, the RIDASCREEN assays could not be considered further.

5.4 The committee questioned whether the data from the studies included in the clinical-effectiveness review were generalisable to the population in the decision problem for this assessment. It noted that many of the studies were done in secondary care and included people with higher-risk symptoms than those outlined in NICE's guideline on [suspected cancer](#). The committee heard from clinical specialists that although the populations in the studies were likely to have a higher prevalence of colorectal cancer, the data provide evidence that faecal immunochemical tests are likely to be highly sensitive for detecting haemoglobin in faecal samples. The committee concluded that although the differences in the populations introduced some uncertainty into the analysis it was reasonable to include the data in the review.

5.5 The committee discussed the diagnostic accuracy data in the included studies. Many reported diagnostic accuracy estimates at multiple thresholds and showed that there was a clear threshold effect; when lower thresholds were used the sensitivity of the test increased, but the specificity decreased. The committee noted that the external assessment group (EAG) had used the diagnostic accuracy data to establish the threshold for the best diagnostic performance. The committee heard from clinical specialists that they supported the EAG's conclusion that a threshold of 10 micrograms of haemoglobin (Hb)/g faeces seemed to give the best diagnostic performance for ruling out colorectal cancer. It also heard that using a threshold lower than 10 micrograms Hb/g faeces would create more variability in test performance because the assays are known to be more imprecise in their lower measuring

range, and the availability of quality control materials to validate the detection of low levels of haemoglobin may also be limited. The committee concluded that using a threshold of 10 micrograms Hb/g faeces gave the test sufficient sensitivity to reliably rule out colorectal cancer in primary care.

5.6 The committee considered the consequences of false-positive faecal immunochemical test results in practice. It heard from clinical specialists that using faecal immunochemical tests in primary care to triage suspected colorectal cancer referrals could result in unnecessary colonoscopy referrals. Data in the clinical-effectiveness review suggested that around 200 of every 1,000 people tested do not have colorectal cancer but are referred for colonoscopy. The committee noted that the tests detect a marker of colorectal cancer (haemoglobin), which could also be associated with a range of other conditions. Data from studies reporting diagnostic accuracy for multiple target conditions in the same population suggested that up to 28.9% of people with a false-positive faecal immunochemical test result for colorectal cancer had bowel pathology, such as inflammatory bowel disease or high-risk adenoma. The committee concluded that it was plausible that the number of false-positive results that occur when using the tests to rule out colorectal cancer could be partially offset by detecting other treatable bowel pathology.

5.7 The committee noted that the review did not find any data that directly compared the OC Sensor, HM-JACKarc or FOB Gold assays. Further, it noted that the review had found substantially less data for the FOB Gold assay so the EAG could not establish the optimal threshold for this test. The committee therefore examined whether the conclusions reached based on data from the OC Sensor and HM-JACKarc assays could be extended to the FOB Gold assay. It heard from clinical specialists that the 3 assays

were likely to perform similarly in detecting haemoglobin in faecal samples. It also heard that the FOB Gold assay was compatible with a range of clinical chemistry analysers, which may be an advantage for some laboratories. The committee concluded that there was greater uncertainty in the clinical effectiveness of the FOB Gold assay but that the available data suggested that it was likely to perform similarly to the OC Sensor and HM-JACKarc assays in practice.

- 5.8 The committee discussed the possibility of faecal immunochemical tests performing differently in the population subgroups outlined in the decision problem. It heard from clinical specialists that it is plausible that the diagnostic accuracy of faecal immunochemical tests will differ according to age and sex because it is thought that women have lower levels of faecal haemoglobin than men and that levels are higher in older people. The committee noted that only 1 study reported data for men and women separately; this study showed that faecal immunochemical testing was more sensitive in men, but more specific in women. No studies were found that presented data by age. It also heard that both faecal immunochemical tests and guaiac-based faecal occult blood tests may have high false-positive rates in people who are taking medicines that increase their risk of gastrointestinal bleeding, such as oral anticoagulants, antiplatelets or aspirin, but no data were available for this group. The committee concluded that there were insufficient data at present to determine whether different thresholds are needed for women and older people, or whether faecal immunochemical tests help with clinical decision-making when people are taking medicines known to cause gastrointestinal bleeding.

Cost effectiveness

- 5.9 The committee considered the cost-effectiveness analyses for the OC Sensor, HM-JACKarc and FOB Gold assays. It noted that 2 comparators had been included; guaiac-based faecal occult blood testing and no triage (that is, direct referral to colonoscopy). The committee discussed which comparator was the most appropriate. It heard from clinical specialists that guaiac-based faecal occult blood testing is no longer done by most clinical chemistry laboratories so primary care does not have access to this test. It also heard that people in the population outlined in the decision problem were unlikely to be directly referred for colonoscopy, and that a watch-and-wait strategy is most often used to monitor their condition. The committee heard from the EAG that a watch-and-wait strategy had not been included in the model because there were not enough data available to characterise the variations in clinical decision-making in this group. The committee concluded that, although the model did not fully capture current practice, the comparisons it made reflected the best available data for the population included in the assessment.
- 5.10 The committee discussed the likely consequences of false-negative results and whether they could affect a person's prognosis by delaying their diagnosis of colorectal cancer. It noted that the economic model assumed that all people with a false-negative result were subsequently diagnosed within 12 months. It heard from clinical and patient specialists that delayed diagnosis could lead to worse outcomes, but clinical specialists advised that if symptoms persisted a referral to secondary care would be made regardless of a previous negative test result. The committee concluded that the analysis had sufficiently captured the likely prognostic implications of false-negative test results.

- 5.11 The committee considered the assumptions made in the model when comparing faecal immunochemical tests with guaiac-based faecal occult blood tests. It noted that none of the studies in the clinical-effectiveness review compared faecal immunochemical tests and guaiac-based faecal occult blood tests, so indirect comparisons had to be modelled. The committee discussed the diagnostic accuracy estimates used in the model (see [table 4](#)) and noted that they suggested that the faecal immunochemical tests were more sensitive than guaiac-based faecal occult blood tests. It heard from clinical specialists that the conclusions drawn from the indirect comparisons were supported by direct comparative data from bowel cancer screening programmes, which have shown that faecal immunochemical tests are more sensitive than guaiac-based faecal occult blood tests. The committee concluded that the assumptions made about the accuracy of guaiac-based faecal occult blood tests were reasonable.
- 5.12 The committee considered the base-case analysis. It noted that the EAG had not included the FOB Gold assay in this analysis because no data were available for the accuracy of the assay at a threshold of 10 micrograms Hb/g faeces. In the comparison with guaiac-based faecal occult blood test both the OC Sensor and the HM-JACKarc assays were cost effective, with probabilistic ICERs of £5,040 and £14,600 per QALY respectively. Both assays were also cost effective when compared with no triage, with the HM-JACKarc dominating (that is, it was more effective and less expensive) and the OC Sensor having an ICER of £2,580,000 saved per QALY lost. The fully incremental base-case analysis suggested that the OC Sensor was more cost effective than the HM-JACKarc, but the committee noted that this comparison was driven by small differences in both costs and QALYs. The committee considered the scenario analyses that included the FOB Gold assay and noted that although there was greater

uncertainty in the clinical effectiveness of this technology it appeared to be cost effective, with an ICER of £15,700 per QALY gained when compared with guaiac-based faecal occult blood testing at a threshold of 6.8 micrograms Hb/g faeces. The committee concluded that the OC Sensor, HM-JACKarc and FOB Gold assays had the potential to be cost-effective options for triaging referrals in primary care for people with symptoms but a low risk of colorectal cancer.

5.13 The committee considered the drivers behind the cost savings seen when the faecal immunochemical tests were compared with no triage and noted that a reduction in colonoscopy was a key parameter. It was aware that the comparison made between faecal immunochemical tests and no triage assumes that all people have either colonoscopy or CT colonography to investigate the cause of their symptoms. The committee discussed colonoscopy capacity and whether the cost savings seen in the analysis for this comparison would be realised in practice. It heard from clinical specialists that colonoscopy capacity is very limited in many areas, and in practice it would be unlikely that all people who are at a low risk of colorectal cancer would be referred for colonoscopy. The committee concluded that the cost savings seen in comparisons made between faecal immunochemical tests and no triage could not be considered robust.

5.14 The committee discussed the uncertainties in the cost-effectiveness analysis and noted that the cost effectiveness of faecal immunochemical tests was sensitive to the prevalence of colorectal cancer. This parameter drives the accuracy of the tests and consequently the costs and resource use. It noted the scenario analyses that used prevalence values of 3% and 5.4% compared with 1.5% in the base case. The results of these scenario analysis showed that when the prevalence was increased the faecal

immunochemical tests became more cost effective when compared with guaiac-based faecal occult blood testing, and when the prevalence of colorectal cancer was decreased the faecal immunochemical tests became less cost effective. The committee therefore considered that if the faecal immunochemical tests are used in a wider population in practice, the prevalence of colorectal cancer will be reduced and the tests may no longer be cost effective. The committee concluded that the tests are likely to be cost effective when used to rule out colorectal cancer if a GP is considering a suspected colorectal cancer referral for a patient. Further, it considered that the results of the test should be used, alongside clinical judgement and the results of any other testing, to determine whether a referral is made using a suspected cancer pathway for an appointment within 2 weeks or a routine outpatient referral.

Other considerations

- 5.15 The committee discussed the possible advantages of using quantitative faecal immunochemical tests. It heard that the ability of the tests to report the concentration of faecal haemoglobin instead of providing a semi-quantitative positive or negative result could have additional clinical uses. It heard from a clinical specialist that, in some areas of Scotland, quantitative faecal immunochemical tests have been adopted to triage referrals from primary care and that the faecal haemoglobin concentration is being used in secondary care to decide who should have a colonoscopy most urgently. The committee also heard that the prognostic-risk scoring tools, highlighted in the clinical-effectiveness review (section 4.20) are a growing area of research that aims to produce validated tools that can identify people at increased risk of colorectal cancer using variables such as age, sex and faecal haemoglobin concentration. The committee concluded that the development of risk-prediction

rules may further refine the use of faecal immunochemical tests in primary care.

- 5.16 The committee noted that the NHS bowel cancer screening programme is adopting faecal immunochemical tests as a replacement for guaiac-based faecal occult blood tests. It considered that there may be instances when people, who have recently had a negative screening result, may get a positive result in primary care after reporting symptoms because of the use of different thresholds in the 2 clinical scenarios. The committee concluded that practices adopting faecal immunochemical tests as a triage tool should take this into account when developing their implementation plans, and ensure that information to explain the different thresholds and their consequences is available for people who have recently participated in the bowel cancer screening programme.

Research considerations

- 5.17 The committee considered that practices adopting the faecal immunochemical tests to triage referral to secondary care should audit their outcomes. Possible outcomes to audit include the number of people referred using a suspected cancer pathway for an appointment within 2 weeks and how many of them were diagnosed with colorectal cancer. The committee noted that Cancer Research UK is planning an audit in the south west of England to collect information on how people at low-risk are assessed in primary care.

6 Draft recommendation for further research

- 6.1 The committee considered that further research is needed to determine whether faecal haemoglobin levels are influenced by age, sex and medicines that increase the risk of gastrointestinal bleeding. It noted that these data could be used to further develop

risk scores that include age, sex and faecal haemoglobin concentration in their range of variables.

7 Implementation

NICE intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

In addition NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in [section 6](#) into its guidance research recommendations database (available on the [NICE website](#)) and highlight these recommendations to public research bodies.

8 Review

NICE reviews the evidence 3 years after publication to identify any new relevant evidence. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, diagnostics advisory committee
November 2016

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland

Chair, diagnostics advisory committee

Dr Mark Kroese

Vice Chair, diagnostics advisory committee and Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Ron Akehurst

Professor in Health Economics, School of Health and Related Research (SchARR), University of Sheffield

Mr John Bagshaw

In-vitro Diagnostics Consultant

Dr Sue Crawford

GP Principal, Chillington Health Centre

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray

Consultant Microbiologist, Birmingham Children's Hospital

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Patrick McGinley

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells
NHS Trust

Dr Michael Messenger

Deputy Director and Scientific Manager NIHR Diagnostic Evidence
Co-operative, Leeds

Mrs Alexandria Moseley

Lay member

Dr Peter Naylor

GP, Chair Wirral Health Commissioning Consortia

Dr Dermot Neely

Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon
Tyne NHS Trust

Dr Simon Richards

VP Regulatory Affairs, EME, Alere Inc

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of
York

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist, Sheffield Teaching Hospitals
Foundation Trust

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas Hospital

Specialist committee members

Mr Ian Danks

Lay member

Miss Farhat Din

Senior Lecturer and Honorary Consultant Surgeon, The University of Edinburgh

Dr Ian Godber

Consultant Clinical Scientist and Clinical Lead for Biochemistry, Monklands Hospital NHS Lanarkshire

Dr Robert Logan

Consultant Gastroenterologist, King's College Hospital NHS Foundation Trust

Dr Sophie Nelson

GP, Kenmore Medical Centre, Wilmslow

Dr Paul O'Toole

Consultant Gastroenterologist, Royal Liverpool University Hospital

Mrs Judith Strachan

Consultant Clinical Scientist, King's Cross Hospital, NHS Tayside

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Rebecca Albrow

Topic Lead

Frances Nixon

Technical Adviser

Robert Fernley

Project Manager

10 Sources of evidence considered by the committee

The diagnostics assessment report 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.

Registered stakeholders

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

Manufacturers 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 Nursing
- Royal College of Pathologists

- Royal College of Physicians

Research groups

- Cancer Research UK

Associated guideline groups

None

Others

- Birmingham Quality (UK NEQAS)
- BIVDA
- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- NHS England
- UK National Screening Committee
- Welsh Government

ISBN: