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Abstract

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

Marie Westwood,[1]* Isaac Corro Ramos,[2] Shona Lang,[1] Marianne Luyendijk,[3] Remziye Zaim,[3] Lisa Stirk,[1] Maiwenn Al,[3] Nigel Armstrong[1] and Jos Kleijnen[4]

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Background: Colorectal cancer (CRC) is the third most common cancer in the UK. Presenting symptoms that can be associated with CRC usually have another explanation. Faecal immunochemical tests (FITs) detect blood that is not visible to the naked eye and may help to select patients who are likely to benefit from further investigation.

Objectives: To assess the effectiveness of FITs [OC-Sensor (Eiken Chemical Co./MAST Diagnostics, Tokyo, Japan), HM-JACKarc (Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan), FOB Gold (Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy), RIDASCREEN Hb or RIDASCREEN Hb/Hp complex (R-Biopharm, Darmstadt, Germany)] for primary care triage of people with low-risk symptoms.

Methods: Twenty-four resources were searched to March 2016. Review methods followed published guidelines. Summary estimates were calculated using a bivariate model or a random-effects logistic regression model. The cost-effectiveness analysis considered long-term costs and quality-adjusted life-years (QALYs) that were associated with different faecal occult blood tests and direct colonoscopy referral. Modelling comprised a diagnostic decision model, a Markov model for long-term costs and QALYs that were associated with CRC treatment and progression, and a Markov model for QALYs that were associated with no CRC.

Results: We included 10 studies. Using a single sample and 10 µg Hb/g faeces threshold, sensitivity estimates for OC-Sensor [92.1%, 95% confidence interval (CI) 86.9% to 95.3%] and HM-JACKarc (100%, 95% CI 71.5% to 100%) indicated that both may be useful to rule out CRC. Specificity estimates were 85.8% (95% CI 78.3% to 91.0%) and 76.6% (95% CI 72.6% to 80.3%). Triage using FITs could rule out CRC and avoid colonoscopy in approximately 75% of symptomatic patients. Data from our systematic review suggest that 22.5–93% of patients with a positive FIT and no CRC have other significant bowel pathologies. The results of the base-case analysis suggested minimal difference in QALYs between all of the strategies; no triage (referral straight to colonoscopy) is the most expensive. Faecal immunochemical testing was cost-effective (cheaper and more, or only slightly less, effective) compared

with no triage. Faecal immunochemical testing was more effective and costly than guaiac faecal occult blood testing, but remained cost-effective at a threshold incremental cost-effectiveness ratio of £30,000. The results of scenario analyses did not differ substantively from the base-case. Results were better for faecal immunochemical testing when accuracy of the guaiac faecal occult blood test (gFOBT) was based on studies that were more representative of the correct population.

Limitations: Only one included study evaluated faecal immunochemical testing in primary care; however, all of the other studies evaluated faecal immunochemical testing at the point of referral. Further, validation data for the Faecal haemoglobin, Age and Sex Test (FAST) score, which includes faecal immunochemical testing, showed no significant difference in performance between primary and secondary care. There were insufficient data to adequately assess FOB Gold, RIDASCREEN Hb or RIDASCREEN Hb/Hp complex. No study compared FIT assays, or FIT assays versus gFOBT; all of the data included in this assessment refer to the clinical effectiveness of individual FIT methods and *not* their comparative effectiveness.

Conclusions: Faecal immunochemical testing is likely to be a clinically effective and cost-effective strategy for triaging people who are presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC. Further research is required to confirm the effectiveness of faecal immunochemical testing in primary care practice and to compare the performance of different FIT assays.

Study registration: This study is registered as PROSPERO CRD42016037723.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

Adenoma A benign tumour of the epithelial tissue that, over time, may transform to become malignant.

Colonoscopy Endoscopic examination of the large intestine and distal small intestine with a charge-coupled device camera or a fibre-optic camera.

Colorectal cancer Cancer of the colon or rectum (large intestine).

Computed tomography colonography A medical imaging procedure using X-rays to produce two- and three-dimensional images of the colon and distal small intestine.

Cost-effectiveness analysis An economic analysis that converts effects into health terms and describes the costs for additional health gain.

Decision modelling A mathematical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions.

Faecal immunochemical test An immunochemical method of detecting blood in the faeces, which specifically detects the globin moiety of human haemoglobin.

Faecal occult blood Blood in the faeces that is not visibly apparent.

False negative Incorrect negative test result – number of diseased persons with a negative test result.

False positive Incorrect positive test result – number of non-diseased persons with a positive test result.

Guaiac faecal occult blood test A chemical method of detecting blood in the faeces that utilises the pseudo-peroxidase activity of haem to detect the haem complex.

Incremental cost-effectiveness ratio The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.

Index test The test whose performance is being evaluated.

Inflammatory bowel disease A group of inflammatory diseases of the colon and small intestine (e.g. Crohn's disease, ulcerative colitis).

Markov model An analytic method that is particularly suited to modelling repeated events or the progression of a chronic disease over time.

Meta-analysis Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

Meta-regression Statistical technique used to explore the relationship between study characteristics and study results.

Negative predictive value The probability of non-disease among persons with a negative test result.

Opportunity costs The cost of forgone outcomes that could have been achieved through alternative investments.

Positive predictive value The probability of disease among persons with a positive test result.

Probabilistic sensitivity analysis A method of quantifying the uncertainty in a mathematical model, such as a cost-effectiveness model.

Publication bias Bias arising from the preferential publication of studies with statistically significant results.

Quality of life An individual's emotional, social and physical well-being and their ability to perform the ordinary tasks of living.

Quality-adjusted life-year A measure of health gain, used in economic evaluations, in which survival duration is weighted or adjusted by the patient's quality of life during the survival period.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold.

Reference standard The best currently available method for diagnosing the target condition. The index test is compared against this to allow calculation of estimates of accuracy.

Regression analysis A statistical method for estimating relationships among variables.

Sensitivity Proportion of people with the target disorder who have a positive test result.

Specificity Proportion of people without the target disorder who have a negative test result.

True negative Correct negative test result – number of non-diseased persons with a negative test result.

True positive Correct positive test result – number of diseased persons with a positive test result.

List of abbreviations

AACC	American Association for Clinical Chemistry
AJCC	American Joint Committee on Cancer
ARIF	Aggressive Research Intelligence Facility
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CCT	controlled clinical trial
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CRC	colorectal cancer
CRD	Centre for Reviews and Dissemination
CT	computed tomography
CTC	computed tomography colonography
DARE	Database of Abstracts of Reviews of Effects
DDW	Digestive Disease Week
EQ-5D	EuroQol-5 Dimensions
FAST	Faecal haemoglobin, Age and Sex Test
FIT	faecal immunochemical test
FN	false negative
FOBT	faecal occult blood test
FP	false positive
GDG	guideline development group
gFOBT	guaiac faecal occult blood test
GI	gastrointestinal
GP	general practitioner
Hb	haemoglobin
Hp	haptoglobin
HRA	high-risk adenoma
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HSROC	hierarchical summary receiver operating characteristic
HTA	Health Technology Assessment
IBD	inflammatory bowel disease
ICER	incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
LY	life-year
MeSH	medical subject heading
NCIN	National Cancer Intelligence Network
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPV	negative predictive value
ONS	Office for National Statistics
PPV	positive predictive value
PROBAST	Prediction model study Risk Of Bias Assessment Tool
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Service Research Unit
QALY	quality-adjusted life-year
RCT	randomised controlled trial

ROC	receiver operating characteristic	TN	true negative
SD	standard deviation	TP	true positive
SE	standard error	UEGW	European Gastroenterology Federation Week
SIGN	Scottish Intercollegiate Guidelines Network	WHO	World Health Organization
SROC	summary receiver operating characteristic		

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Bowel (colorectal) cancer is the third most common cancer in the UK. Symptoms, such as anaemia, abdominal pain and altered bowel habit, can be early warnings of bowel cancer, but these symptoms usually have another explanation. In order to be sure whether or not someone has bowel cancer, hospital tests, such as colonoscopy, are needed. Because colonoscopy can be unpleasant and carries a small risk of heavy bleeding or tearing of the bowel, it is important to find tests that can help to select people who really need to have colonoscopy, that is, those who are more likely to have bowel cancer and other serious lower gastrointestinal disease, including inflammatory bowel disease.

The faecal immunochemical test (FIT) for haemoglobin detects blood in the faeces that is not visible to the naked eye.

This report looks at whether or not faecal immunochemical testing should be offered to people reporting bowel symptoms to their doctor who are considered to be at low risk of having bowel cancer.

We included 10 studies that looked at how well the results of faecal immunochemical testing can predict whether or not bowel cancer is found when a person has a colonoscopy examination. Research indicates that a negative FIT result could be used to reliably determine that a person does not have bowel cancer in around three-quarters of people with low-risk bowel symptoms. Using faecal immunochemical testing could therefore reduce the number of people who do not have bowel cancer undergoing 'unnecessary' colonoscopy. Although most people who have a positive FIT result and low-risk bowel symptoms do not have bowel cancer, other bowel diseases are often found when these people are sent for colonoscopy examination.

Because there has been no research comparing different brands of FITs, we cannot know whether or not any one test is better than another.

Scientific summary

Background

The primary indication for this assessment is the use of tests for the presence of occult blood in the faeces as a triage step in the investigation of people presenting in primary care settings with lower abdominal symptoms, in whom investigation for possible colorectal cancer (CRC) is being considered.

Quantitative faecal immunochemical tests (FITs) use antibodies that specifically recognise the globin of human haemoglobin (Hb) to determine the amount of Hb that is present in a faecal sample. Four FIT assays for Hb [OC-Sensor (Eiken Chemical Co./MAST Diagnostics, Tokyo, Japan), HM-JACKarc (Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan), FOB Gold (Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy), RIDASCREEN Hb, R-Biopharm, Darmstadt, Germany)] and one FIT assay for human Hb–haptoglobin (Hp) complex (RIDASCREEN Hb/Hp complex, R-Biopharm) are currently available for use in the UK NHS in England and Wales. Quantitative FIT assays the estimation of quantities of blood that are not detectable by normal visual inspection.

Faecal immunochemical testing has been approved for the Scottish Bowel Screening Programme and has recently been approved for use in the NHS Bowel Cancer Screening Programme in England. This assessment considers the clinical effectiveness and cost-effectiveness of FIT assays, used at various thresholds, in symptomatic populations.

Objectives

To assess the clinical effectiveness and cost-effectiveness of testing for the presence of occult blood in faeces, using quantitative faecal immunochemical testing, as a triage test, for people presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC.

Methods

Assessment of clinical effectiveness

Thirteen databases, including MEDLINE and EMBASE, research registers and conference proceedings were searched to March 2016. Search results were screened for relevance independently by two reviewers. Full-text inclusion assessment, data extraction and quality assessment were conducted by one reviewer and checked by a second. Study quality was assessed using QUADAS-2 and PROBAST (Prediction model study Risk Of Bias Assessment Tool). The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% confidence intervals (CIs) and prediction regions around the summary points, and to derive HSROC curves for meta-analyses involving four or more studies. For meta-analyses with fewer than four studies, we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression. Analyses were conducted separately for each FIT assay, threshold and target condition {CRC, advanced neoplasia [CRC or high-risk adenoma (HRA)] or significant bowel disease (CRC or HRA or inflammatory bowel disease)} for which data were available.

Assessment of cost-effectiveness

A de novo health economic model was developed to explore the cost-effectiveness of using faecal immunochemical testing for Hb as a triage step in the investigation of symptomatic people presenting in primary care who are at low risk of CRC. The cost-effectiveness of faecal immunochemical testing was

compared with guaiac faecal occult blood tests (gFOBTs) and no triage (referral straight to colonoscopy). The model consists of three parts: a decision model reflecting the diagnosis of colorectal cancer; a Markov state-transition model to estimate long-term costs and the effects [life-years (LYs) and quality-adjusted life-years (QALYs)] associated with the treatment and progression of CRC; and a Markov state-transition model to estimate the LYs and QALYs associated with those who do not have CRC. The following strategies were included in the main economic analysis:

- triage using OC-Sensor at a threshold of 10 µg Hb/g faeces
- triage using HM-JACKarc at a threshold of 10 µg Hb/g faeces
- triage using guaiac faecal occult blood testing
- no triage (referral straight to colonoscopy).

The model was largely based on that used in the National Institute for Health and Care Excellence (NICE) guideline [National Collaborating Centre for Cancer. *Suspected Cancer*: *Recognition and Referral*. NG12. London: NCC-C; 2015. URL: www.nice.org.uk/guidance/ng12/evidence/full-guidance-74333341 (accessed 13 January 2016)], but with diagnostic accuracy data coming from the systematic review that was used to inform the assessment of effectiveness. When available, data were obtained from the most recent published sources, although expert opinion was required to inform some parameters. Any differences in costs between the tests in patients without CRC were assumed to occur only in the first year. Any differences in life expectancy between tests for patients without CRC were assumed to be due only to difference in mortality due to colonoscopy/computed tomography colonography (CTC). A negative FIT or gFOBT results in a watchful waiting strategy, in which a colonoscopy/CTC will be performed when symptoms persist, which is assumed to occur with all patients with CRC. All of the unit cost data on faecal immunochemical testing were obtained from manufacturers where supplied.

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

Results

Assessment of clinical effectiveness

Ten studies (25 publications and two unpublished manuscripts) were included in the systematic review. The main potential sources of bias in the included studies related to patient spectrum and patient flow (numbers of patients who did not return a FIT sample or who were subsequently excluded). All of the included studies had concerns about the applicability of the population, as no study reported data for a population that exactly matched that defined in the scope for this assessment.

When faecal immunochemical testing was based on a single faecal sample and a threshold of 10 µg Hb/g faeces, sensitivity estimates indicated that a negative result using either OC-Sensor and HM-JACKarc may be considered adequate to rule out CRC; the summary estimate of sensitivity for OC-Sensor was 92.1% (95% CI 86.9% to 95.3%), based on four studies, and the only study of HM-JACKarc to assess the 10 µg Hb/g faeces threshold reported a sensitivity of 100% (95% CI 71.5% to 100%). The corresponding specificity estimates were 85.8% (95% CI 78.3% to 91.0%) and 76.6% (95% CI 72.6% to 80.3%), respectively. (Confidential information has been removed.)

Where a lower diagnostic threshold was considered, that is, the target condition included HRA as well as CRC, the rule-out performance of all FIT methods was reduced. For faecal immunochemical testing based on a single faecal sample and a threshold of 10 µg Hb/g faeces, the sensitivity estimates indicated that neither a negative OC-Sensor nor a negative HM-JACKarc FIT would be likely to be considered to have adequate rule-out performance; the summary estimate of sensitivity for OC-Sensor was 62.9% (95% CI 55.9% to 69.4%), based on three studies, and the estimate of sensitivity for HM-JACKarc was 70.0%

(95% CI 50.6% to 85.3%), based on one study. The corresponding specificity estimates were 84.6% (95% CI 82.8% to 86.2%) and 77.8% (95% CI 73.8% to 81.4%), respectively.

Triage using faecal immunochemical testing at thresholds of around 10 µg Hb/g faeces has the potential to correctly rule out CRC and avoid colonoscopy in approximately 75% of symptomatic patients. In addition, the relatively high proportion of FIT false positives (FPs) that are observed when the target condition is CRC may be mitigated by the detection of other bowel pathologies in these patients. Based on data from the studies included in our systematic review, between 22.5% and 93% of patients with a positive FIT and no CRC will have other significant bowel pathologies.

No studies were identified which assessed the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients.

No studies were identified which directly compared the performance of different FIT assays, or which compared one or more FIT assays with a gFOBT method.

Assessment of cost-effectiveness

The results of the base-case analysis suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the no-triage strategy (referral straight to colonoscopy) is the most expensive. Overall, faecal immunochemical testing was cost-effective when compared with no triage. This was either because the latter was dominated (less effective and more costly) or because faecal immunochemical testing was slightly less effective, but cheaper, than no triage. In this case the cost savings could be said to 'outweigh' the slight loss in QALYs. When the comparator was guaiac faecal occult blood testing, the cost-effectiveness results showed that faecal immunochemical testing was more effective and more costly than guaiac faecal occult blood testing, but the incremental cost-effectiveness ratios (ICERs) obtained were below the common threshold ICER of £30,000 and thus faecal immunochemical testing remained cost-effective.

The results of the different scenario analyses did not differ substantively from the base-case results. The scenarios for which the accuracy estimates for guaiac faecal occult blood testing were based on studies that were considered more representative of the population of this diagnostic assessment were more favourable than the base-case with regard to faecal immunochemical testing. In only two scenarios would faecal immunochemical testing not be considered cost-effective because the ICER exceeded the £30,000 threshold. The highest ICER was obtained when OC-Sensor was compared with guaiac faecal occult blood testing when a threshold of any detectable Hb was assumed for faecal immunochemical testing (£65,192). This was expected, as reducing the threshold for FIT results in the test being less effective in avoiding colonoscopies, that is, this threshold is associated with the highest number of FPs. When HM-JACKarc was compared with guaiac faecal occult blood testing in the scenario with high mortality due to colonoscopy the ICER was £45,271.

Conclusions

Implications for service provision

There is evidence to suggest that triage using faecal immunochemical testing, when used at a threshold of 10 µg Hb/g faeces for OC-Sensor or HM-JACKarc, may be sufficient to rule out CRC in symptomatic patients. In addition, the relatively high proportion of FIT FPs observed when the target condition is CRC may be mitigated by the potential to diagnose other bowel pathologies in these patients. There was insufficient evidence to adequately assess the diagnostic performance of FOB Gold, RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients. Similarly, there was no direct evidence about the comparative performance of different FIT assays, or faecal immunochemical testing versus guaiac faecal occult blood testing.

The base-case cost-effectiveness results suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the no-triage strategy (referral to colonoscopy) is the most expensive. Overall, faecal immunochemical testing was cost-effective when compared against no triage or guaiac faecal occult blood testing. The results of the different scenario analyses did not differ substantially from the base-case results. However, the scenarios for which the accuracy estimates for guaiac faecal occult blood testing were based on studies that were considered more representative of the population of this diagnostic assessment were more favourable than the base-case scenario with regard to faecal immunochemical testing. The results of our analysis suggest that faecal immunochemical testing could provide a cost-effective (cost-saving) triage option for patients whose symptoms are not considered high risk for CRC.

Suggested research priorities

New studies are needed to fully evaluate the performance of faecal immunochemical testing in the setting (primary care) and population (symptomatic patients who are at low risk of CRC, as defined in NG12) specified in the scope for this assessment. Further research (diagnostic cohort studies or multivariable prediction modelling studies) is needed to fully explore possible variation in the performance of faecal immunochemical testing in relevant subgroups (e.g. age and sex) and explore the possible advantages of using faecal immunochemical testing as part of a risk score. Studies that can fully explore the potential benefits of faecal immunochemical testing in symptomatic patients, including those relating to diagnoses other than CRC, are also likely to be informative. This issue may be particularly important in younger patients, where the prevalence of CRC is lowest and other diagnoses are more likely.

Study registration

This study is registered as PROSPERO CRD42016037723.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Objective

The overall objective of this project is to summarise the evidence on the clinical effectiveness and cost-effectiveness of using quantitative faecal immunochemical tests (FITs) as a triage test for people presenting, in primary care settings, with lower abdominal symptoms, who are at low risk for colorectal cancer (CRC) according to the criteria defined in the 2015 National Institute for Health and Care Excellence (NICE) guideline (NG12).[1] Use of occult blood testing in the faeces has been recently recommended for this population; this assessment will consider the clinical effectiveness and cost-effectiveness of quantitative faecal immunochemical testing as a replacement for guaiac testing. The following research questions have been defined to address the review objective:

- What is the clinical effectiveness of faecal immunochemical testing compared with guaiac faecal occult blood testing or no triage, for achieving appropriate referral for further investigation within the 2-week suspected cancer referral target?
- What is the comparative accuracy of different quantitative FIT assays and guaiac faecal occult blood testing, for which CRC determined by colonoscopy (the reference standard method) is the target condition?
- What is the diagnostic accuracy of different quantitative FIT assays, where CRC determined by colonoscopy (the reference standard method) is the target condition?
- What is the cost-effectiveness of using faecal immunochemical testing for the presence of occult blood as a triage step in the investigation of symptomatic patients for suspected CRC compared with the recent recommendation of guaiac faecal occult blood testing and no triage (referral straight to colonoscopy)?

Note

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Chapter 2 Background and definition of the decision problem(s)

Population

The primary indication for this assessment is the use of tests for the presence of occult blood in the faeces as a triage step in the investigation of people presenting in primary care settings, with lower abdominal symptoms in whom investigation for possible CRC is being considered. NICE guidance on suspected cancer: recognition and referral (NG12[1]) recommends the use of guaiac testing for occult blood in the faeces as a triage step before referral for secondary care investigations, in specified symptomatic patient groups – people aged:

- ≥ 50 years, who have unexplained abdominal pain or weight loss
- < 60 years, who have changes in their bowel habit or iron-deficiency anaemia
- ≥ 60 years, who have anaemia in the absence of iron deficiency.

This assessment will consider the clinical effectiveness and cost-effectiveness of using quantitative faecal immunochemical testing for haemoglobin (Hb) as a triage test. The clinical effectiveness and cost-effectiveness of triage testing using faecal immunochemical testing will be considered for all people presenting, in primary care settings, with lower abdominal symptoms who require investigation for possible CRC, not limited to the specific groups detailed in NG12.[1]

Colorectal cancer is the third most common cancer in the UK population overall and in people aged ≥ 50 years, after breast cancer and lung cancer for females and prostate cancer and lung cancer for males. The most common cancers differ for younger age groups. The Office for National Statistics (ONS) cancer registration data for 2013 showed approximately 35,000 new cases of CRC in England (18,839 males and 14,926 females).[2] The incidence of CRC was 87 cases per 100,000 males and 52 cases per 100,000 females; the age-standardised incidence rate was 54.4% higher in males than in females and has increased for both males and females over the last 10 years.[2] CRC accounted for approximately 11.5% of all new cancers diagnosed in 2013 (12.6% in males and 10.4% in females) and increasing with age to 14.2% of cancers in males aged ≥ 80 years and 15.2% in females aged ≥ 80 years.[2] The age-standardised 1-year survival rates for men and women who were diagnosed with CRC between 2009 and 2013, and followed up to 2014, were 77.5% and 75.8%, respectively.[3] The corresponding 5-year survival rates were 58.5% and 58.2%, respectively.[3] Survival rates for CRC have not changed substantively since the previous data collection period (2008–12).

The UK NHS Bowel Cancer Screening Programme in England currently utilises guaiac faecal occult blood testing, but faecal immunochemical testing has been recently recommended by the UK National Screening Committee, has been piloted for national roll-out and recommended by European Commission guidelines.[4,5] However, studies assessing the effectiveness of faecal immunochemical testing or comparing the performance of faecal immunochemical testing and guaiac faecal occult blood testing in asymptomatic population-based screening for CRC will not be included in this assessment. This is because the prevalence of CRC is likely to be higher in a population with even relatively low-risk symptoms than in the general population without symptoms that are eligible for screening, and faecal immunochemical testing used for screening applications will generally use higher cut-off faecal Hb concentrations than would be used for triage of people with symptoms. The cost-effectiveness modelling used to inform NG12[1] based its estimate of the prevalence of CRC in a low-risk population on the positive predictive value (PPV) of symptoms in 22 studies that were identified as relevant.[6] The PPV of altered bowel habit in men and women aged < 60 years ranged from 0.01 to 15.7, and the base-case analysis used a CRC prevalence estimate that was

at the lower end of this range (1.5%).[6] By comparison, estimating the prevalence of CRC in the general population of England, based on ONS cancer registration and population data, gives approximately 0.065% for the whole population and 0.226% for the screening-eligible age group (60–74 years), that is, those who were most likely to match the population included in screening studies. Furthermore, it has been shown that differences in disease prevalence can affect estimates of test performance; data from 23 meta-analyses, which covered a wide range of clinical conditions, showed changes in sensitivity and specificity estimates of between 0% and 40% from the lowest to the highest prevalence.[7] In relation to faecal immunochemical testing, a recent meta-analysis of 19 studies conducted in average-risk, asymptomatic screening populations reported summary estimates of sensitivity and specificity for CRC of 79% [95% confidence interval (CI) 69% to 86%] and 94% (95% CI 92% to 95%), respectively; however, this analysis pooled data for eight different FIT assays.[8]

The 2015 National Bowel Cancer Audit Report[9] stated that, of all patients diagnosed with CRC in 2014, 55% were diagnosed following a general practitioner (GP) referral and 9% (20% of those in the eligible age range for screening, 60–74 years) were diagnosed through the NHS Bowel Cancer Screening Programme; however, 20% were diagnosed only following an emergency presentation (referral source data were missing for 16% of patients).[9] Treatment with curative intent was possible for more of those patients who were diagnosed through screening (90%) and following GP referral (70%) than those who were presenting as an emergency admission (52%).[9] Work to promote screening uptake and awareness of CRC symptoms is stated as a recommendation, with the aim of reducing the proportion of emergency presentations and improving outcomes. However, increased uptake of screening and increased awareness of, and presentation in, primary care of patients with low-risk symptoms could result in more invasive investigations, such as colonoscopy, being conducted. Estimates from the charity Bowel Cancer UK[10] have suggested that there will be a 10–15% year-on-year increase in demand for colonoscopies, which impacts on the 2-week suspected cancer referral time and NHS capacity.[1] In addition, colonoscopy has associated risks, which include bowel perforation, bleeding, infection and abdominal pain.[11] A recent review reported that most colonoscopies performed in symptomatic patients do not find either CRC or other serious bowel disease, and do not yield changes to the therapeutic approach.[12] The identification of tests that can help to rule out CRC and select people who are more likely to benefit from further investigation is therefore an important goal. It has been suggested that using quantitative immunochemical measurement of faecal Hb concentration to select patients for referral has the potential to reduce unnecessary colonoscopies and provide more accurate classification of patients than traditional, symptoms-based guidelines.[13]

This assessment provides a comprehensive summary of the evidence about the performance of faecal immunochemical testing as a triage test for people, presenting in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1] and for whom a referral for secondary care investigation for possible CRC is being considered.

Intervention technologies

There are two major types of test for the presence of small amounts of blood in faeces: these are guaiac based [guaiac faecal occult blood test (gFOBT)] or immunochemical based (FIT). Guaiac-based methods detect the haem complex, whereas immunochemical methods specifically detect the globin moiety of human Hb.

Guaiac faecal occult blood tests rely on the pseudo-peroxidase activity of haem. A faecal sample is placed on to a paper that is impregnated with guaiac, to which hydrogen peroxide is applied as developer of the test. In the presence of haem, a chemical reaction occurs, yielding a blue- or green-coloured product within seconds. Usually, two faecal samples from each of three separate bowel motions are required.[14] The test is not specific for human blood and will also respond to animal blood, muscle protein and iron supplements. In addition, certain vegetables contain constituents with peroxidase activity, which can lead to false-positive (FP) results, although this can be minimised by waiting for 72 hours before development of the test.

Bleeding gums or medicines that can cause gastrointestinal (GI) irritation or bleeding, for example aspirin and non-steroidal anti-inflammatory drugs, can also result in a FP test result.[15] In addition, a high intake of vitamin C can cause a false-negative (FN) result. In consequence, dietary and medicine restrictions are often imposed prior to testing.[14] gFOBTs are not considered an intervention technology in this assessment.

Faecal immunochemical tests use antibodies that specifically recognise the globin of human Hb. Faecal immunochemical testing has the potential to reduce FPs caused by upper GI bleeding because globin is degraded in the upper GI tract and, therefore, is not present in faecal samples for faecal immunochemical testing to detect. However, haem is resistant to degradation in the upper GI tract and, therefore, this molecule remains in faecal samples and can be detected by guaiac faecal occult blood testing (FP). Usually, only one faecal sample (but sometimes two) is collected and no dietary or medicine restriction is required.[16] Faecal immunochemical testing can be either qualitative or quantitative, and both are available from many different manufacturers with variable designs. Qualitative tests have an end point that is read as positive or negative visually; usually they are of a lateral flow immunochromatographic design, similar to home pregnancy tests. Faecal samples can be collected on to cards, similar to the traditional guaiac faecal occult blood testing, or, more commonly, into specimen collection devices that use probes attached to the lid of the device to transfer a few milligrams of faeces into a few millilitres of stabilising buffer in the device. Each manufacturer sets their own cut-off faecal Hb concentration for a positive test and available qualitative FITs are very different. The need for visual interpretation of the results can introduce interobserver variation. Determination of the presence of a trace line in the test portion of the cassette is a subjective judgement, which can sometimes be difficult. It is difficult to introduce quality control and, if qualitative FITs are used outside laboratories, the stringent recommendations and guidelines for point-of-care tests must be followed. Quantitative faecal immunochemical testing often uses immunoturbidimetric methods to measure the actual concentration of faecal Hb. Analysis is usually automated, facilitating quality management procedures. Most quantitative FITs require 'wet' collection, whereby samples are collected with a probe attached to the lid of the specimen collection device and transferred into a small volume of buffer in the device. The sample may degrade between collection and analysis if not handled properly[14,16] because faecal Hb is very unstable: indeed, faecal samples for faecal immunochemical testing must be collected into the specimen collection devices and cannot be collected by patients into traditional collection pots that are then returned to primary care for onward transport for FIT analysis.

A summary of the product properties of quantitative FIT assays that are available in the NHS in England and Wales, and included in this assessment, is provided in *Table 1*.

Units for faecal immunochemical tests for haemoglobin

Different FITs use a variety of sampling methods, with variation in the mass of faeces collected and the volume and characteristics of the buffer used in the sampling device. These differences make the comparisons of test performance between FIT assay types difficult. FIT results can be expressed as Hb concentration in the sampling device buffer (ng Hb/ml buffer) or as Hb concentration by mass of faeces (µg Hb/g faeces). Initiatives aimed at standardising the units of measurement have resulted in recommendations, from the World Endoscopy Organization Colorectal Cancer Screening Committee's Expert Working Group on 'FIT for Screening'[17] and the Guildford Medical Device Evaluation Centre,[18] that manufacturers should adopt the use of 'µg Hb/g faeces'.

OC-Sensor

OC-Sensor (Eiken Chemical Co./MAST Diagnostics, Tokyo, Japan) is a quantitative faecal immunochemical test. A sample is collected on a probe and inserted immediately into a unique specimen collection device that contains buffer. Analysis is fully automated using the OC-PLEDIA analyser or the OC-Sensor IO analyser – both quantitatively determine the concentrating of Hb present in faecal samples using polyclonal antibodies for human Hb and latex agglutination turbidimetry.[19,20] The OC-PLEDIA can process up to 320 samples per hour, with a capacity of 200 samples per run. The OC-Sensor IO analyser can process up to 88 samples per hour, with a maximum capacity of 20 samples per run.

TABLE 1 Overview of Quantitative Faecal Immunochemical Tests (information supplied to NICE by test manufacturers)

Name	Manufacturer	Test system description	Measurement range	Limit of detection	Limit of quantitation	Cut-off point	Capacity
HM-JACKarc system	Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan	mAb human Hb Automated detection using immunoturbidimetry	7–400 µg Hb/g faeces (7–400 ng Hb/ml buffer)	0.6 µg Hb/g faeces (0.6 ng Hb/ml buffer)	1.25 µg Hb/g faeces (1.25 ng Hb/ml buffer)	10 µg Hb/g faeces (10 ng Hb/ml buffer)	200 samples/hour (maximum capacity of 80 samples/run)
FOB Gold system	Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy	Automated detection using immunoturbidimetry	10 ng Hb/ml buffer to highest calibrator concentration	9.5 ng Hb/ml buffer	13.9 ng Hb/ml buffer	To be determined by each laboratory	Dependent on analyser used
OC-Sensor	Eiken Chemical Co./ MAST Diagnostics, Tokyo, Japan	pAb human Hb Automated detection using immunoturbidimetry	10–1000 ng Hb/ml buffer	IO analyser: 4 µg Hb/g faeces (20 ng Hb/ml buffer) PLEDIA analyser: 2 µg Hb/g faeces (10 ng Hb/ml buffer) Micro analyser: 4 µg Hb/g faeces (20 ng Hb/ml buffer)	IO analyser: 6 µg Hb/g faeces (30 ng Hb/ml buffer) PLEDIA analyser: 2 µg Hb/g faeces (10 ng Hb/ml buffer) Micro analyser: NI	10 µg Hb/g faeces (50 ng Hb/ml buffer)	Dependent on analyser used
RIDASCREEN Hb and Hb/ Hp test	R-Biopharm, Darmstadt, Germany	pAb human Hp, mAb Hb ELISA Manual or automated colour detection	0.65–50 µg Hb/g faeces	0.42 µg Hb/g faeces 0.38 µg Hb/Hp complex/g faeces	0.65 µg Hb/g faeces	2 µg Hb/g faeces 2 µg Hb/Hp complex/g faeces	Manual processing: 91 samples in 150 minutes DYNEX agility®, DYNEX Technologies, Chantilly, VA, USA: 546 samples in 7 hours

ELISA, enzyme-linked immunosorbent assay; mAb, monoclonal antibodies; NI, no information provided; pAb, polyclonal antibodies.

HM-JACKarc system

The HM-JACKarc system (Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan) is a fully automated quantitative faecal immunochemical test. A sample is obtained using the insertion of a probe attached to the cap of the specimen collection device, which is then inserted into a specialised collection tube containing buffer. The system picks up a small volume from the specimen collection devices and adds reagents, including latex reagent pre-coated with antibodies that are specific to the globin moiety of human Hb. Binding of the latex reagent to globin that is present in the faecal sample creates a complex that can be detected using turbidimetry. The system comprises an analyser, faecal sample collection devices (the Extel Hemo-auto MC A device; Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan), latex agglutination reagents (Extel Hemo-Auto HS; Kyowa Medex/Alpha Laboratories Ltd) and buffer (Extel Hemo-auto; Kyowa Medex/Alpha Laboratories Ltd). The test has a measuring range of 7–400 µg Hb/g faeces. The HM-JACKarc analyser can process up to 200 samples per hour, with a maximum capacity of 80 samples per run.[21]

FOB Gold

The FOB Gold system (Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy) is an automated quantitative faecal immunochemical test. Faecal samples are collected on probes, which are immersed immediately into solution within the specimen collection device. This ensures sample stability (14 days at 2–8 °C or 7 days at 15–30 °C). The devices are then placed into an automated analyser. A latex agglutination assay is used which is detected via turbidimetry.[22] The FOB Gold kit has CE (Conformité Européene)-marked applications for a range of clinical chemistry analysers, including those supplied by Roche, Siemens, Beckman Coulter and Abbott. The test has a measuring range of 10 ng/ml to the highest calibrator concentration used, and the instructions for use state that laboratories should establish their own population specific cut-off points. Test throughput is dependent on the analyser that is used to process samples.

RIDASCREEN haemoglobin/haptoglobin complex

The RIDASCREEN Hb test (R-Biopharm, Darmstadt, Germany) is a quantitative human Hb/Hp complex immunochemical test. Detection alone is automated. Samples are collected and kept in chilled storage media. Before analysis, the samples are diluted with extraction buffer and mixed. This can be done manually or using the DSX (DSX®, DYNEX Technologies, Chantilly, VA, USA) automated enzyme-linked immunosorbent assay system. The test is run on a 96-well microtitre plate, which is pre-coated with polyclonal antibodies for human haptoglobin (Hp). The sample solution is applied, followed by a wash step and then application of monoclonal antibody for anti-Hb, which is conjugated to peroxidase. In the presence of a Hb/Hp complex, a sandwich complex forms between the polyclonal and monoclonal antibodies. After further washes, a substrate is added, which reacts with the peroxidase, creating a colour change that can be detected by a plate reader. The values produced by the plate reader are interpreted with the RIDA-SOFT Win.net software (R-Biopharm). The company recommends a cut-off value of > 2 µg/g to determine a positive sample. The test has a limit of detection of 0.42 µg/g. The company suggests that the determination of the Hb/Hp complexes has a diagnostic advantage: as the Hb/Hp complex is resistant to decomposition by acids or proteolytic enzymes, it will maintain in the faeces after long periods in the intestine. Thus, blood admixtures from larger intestinal polyps and colon carcinomas that are located higher up in the intestine can also be recorded with high sensitivity.[23] However, discussion with clinical experts at the scoping stage of this assessment has suggested that this method may also result in an increased number of FPs.

Potential advantages of faecal immunochemical testing

It has been suggested that faecal immunochemical testing may offer improved accuracy compared with guaiac faecal occult blood testing, particularly in relation to the rule-out of CRC. Although most studies do not provide evidence about the performance of the test in symptomatic populations, the idea that faecal immunochemical testing may be associated with improved diagnostic performance relative to guaiac faecal occult blood testing is supported by data from systematic reviews of studies that have been conducted in screening populations.[24,25] A meta-analysis[25] of 18 studies demonstrated that faecal immunochemical testing (OC-Sensor) had a higher sensitivity (87% vs. 47%) with similar specificity (93% vs. 92%) to guaiac

faecal occult blood testing (Hemoccult® test, Beckman Coulter Inc., Brea, CA, USA) for screening for CRC. More recent studies comparing faecal immunochemical testing to guaiac faecal occult blood testing in screening populations have also reported increased sensitivity of faecal immunochemical testing for the detection of CRC of between 31.7% and 61.5%, relative to guaiac faecal occult blood testing, with no change in associated specificity.[26–28] A recent study in symptomatic and asymptomatic patients scheduled for diagnostic colonoscopy reported a smaller difference in sensitivity (14.7%).[29] The results of these studies indicate that faecal immunochemical testing may be associated with a decrease in the number of FN results and potentially missed CRC, relative to guaiac faecal occult blood testing, but not a reduction in FP results (inappropriate referrals).

This assessment systematically reviews the evidence about the performance of faecal immunochemical testing as a triage test for people presenting in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12,[1] and for whom a referral for secondary care investigation for possible CRC is being considered. We have preferentially sought direct comparisons of faecal immunochemical testing and guaiac faecal occult blood testing, to inform comparative cost-effectiveness modelling; however, our assessment also included studies of the diagnostic accuracy of quantitative FIT assays alone (no comparison with gFOBT or other FIT). Where available, data were collected on the use of different faecal Hb concentration cut-off points and/or multiple sampling strategies in order to determine the best way to operationalise FIT use.

A meta-analysis of studies comparing faecal immunochemical testing and guaiac faecal occult blood testing reported that faecal immunochemical testing was associated with a small increase in participation in asymptomatic population-based screening (relative risk 1.16; 95% CI 1.03 to 1.30).[30] Initial reports from the NHS Bowel Cancer Screening Programme in England pilot of faecal immunochemical testing also indicate that faecal immunochemical testing may be associated with increased uptake compared with guaiac faecal occult blood testing (63.9% vs. 54.4% in 60-year-olds who were invited for screening for the first time).[31] We are not aware of any similar studies on testing uptake (or compliance) in symptomatic populations, and the extent to which the acceptability of FIT sample collection would be an issue for people with symptoms is unclear. In order to inform this question, we have collected all of the available data on the return rates for FIT sample collection devices that were issued to participants in the studies that were included in our systematic review.

Comparator

The comparators for this technology are gFOBT[1] and no faecal occult blood triage testing.

Care pathway

Testing for occult blood in faeces in patients presenting to primary care settings

The NHS Bowel Cancer Screening Programme in England offers screening every 2 years to all men and women aged between 60 and 74 years. People aged > 74 years can request a screening kit by contacting the Programme. Screening is currently based on guaiac faecal occult blood testing, but FITs have been recommended by the UK Screening Committee for this purpose and a pilot evaluation has already been completed. FITs are currently recommended as the best non-invasive screening modality in all national and international recommendations.[32]

According to NG12,[1] patients should be referred for an appointment within 2 weeks if they have suspected CRC, defined as:

- aged ≥ 40 years with unexplained weight loss and abdominal pain, or

- aged ≥ 50 years with unexplained rectal bleeding, or
- aged ≥ 60 years with iron-deficiency anaemia or changes in their bowel habit
- tests showing occult blood in their faeces
- having a rectal or abdominal mass
- adults aged < 50 years with rectal bleeding and abdominal pain or change in bowel habit or weight loss or iron-deficiency anaemia.

According to NG12,[1] testing for occult blood in faeces should be offered to adult patients who present with initial symptoms without rectal bleeding who are:

- aged ≥ 50 years with unexplained abdominal pain or weight loss
- aged < 60 years with changes in their bowel habit or iron-deficiency anaemia
- aged ≥ 60 years and having anaemia, even in the absence of iron deficiency.

Further testing following a positive test result for occult blood in faeces

Following a positive test result for occult blood in faeces, people in England are usually offered a colonoscopy within 2 weeks of referral to establish a diagnosis.

The 2011 NICE clinical guideline (CG131)[33] states that patients should be advised that one or more investigations may be necessary to confirm or exclude a diagnosis of CRC. Colonoscopy is offered to patients without significant comorbidity to confirm a diagnosis of CRC; if a suspicious lesion is detected then a biopsy should be performed (unless contraindicated). For people with comorbidities, computed tomography colonography (CTC) can be offered as an alternative to colonoscopy.

The Scottish Intercollegiate Guidelines Network (SIGN) 2011[34] guidance for CRC (updated in 2016) states that patients aged > 40 years who present with new-onset, persistent or recurrent rectal bleeding should be referred for investigation. Review of the patient by a regional clinical genetics service is recommended for accurate risk assessment if family history of CRC is the principal indication for referral for investigation. GPs should perform an abdominal and rectal examination on all patients with symptoms that are indicative of CRC. A positive finding should expedite referral, but a negative rectal examination should not rule out the need to refer. All symptomatic patients should have a full blood count; in cases of anaemia, the presence of iron deficiency should be determined. When CRC is suspected clinically, the whole of the large bowel should be examined:

- Colonoscopy is recommended as a very sensitive method of diagnosing CRC, enabling biopsy and polypectomy.
- CTC can be used as a sensitive and safe alternative to colonoscopy.

Guidelines from clinical professional bodies follow a similar pattern: the Royal College of Radiologists recommends that symptomatic patients with suspected CRC should receive evaluation/diagnosis by imaging studies (colonoscopy, CTC or barium enema);[35] the Association of Coloproctology of Great Britain and Ireland recommends that patients with higher-risk symptoms should be fast-tracked in special clinics or given urgent appointments in routine clinics. Patients so referred should be investigated with sigmoidoscopy (flexible or rigid) plus a high-quality, double-contrast barium enema, or colonoscopy or CTC.[36]

Treatment of colorectal cancer

Following diagnosis and staging, CRC may be treated with surgery, chemotherapy and radiotherapy, or, in some cases, with biological agents such as cetuximab. Treatment is dependent on the stage of the cancer and is described in more detail in CG131.[33]

Chapter 3 Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of faecal immunochemical testing as a triage step in the investigation of people, presenting in primary care, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1] and for whom a referral for secondary care investigation for possible CRC is being considered. Systematic review methods followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[37] and the NICE Diagnostic Assessment Programme manual.[38]

Systematic review methods

Search strategy

Search strategies were based on intervention (FIT assays) and target condition (CRC), as recommended in the CRD guidance for undertaking reviews in health care[37] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[39]

Candidate search terms were identified from target references, browsing database thesauri [e.g. MEDLINE medical subject heading (MeSH) and EMBASE Emtree] and from existing reviews that were identified during initial scoping searches. Strategy development involved an iterative approach, testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies were developed specifically for each database and the keywords associated with faecal immunochemical tests for occult blood were adapted according to the configuration of each database.

No restrictions on language, publication status or date of publication were applied. Searches took into account generic and other product names for the intervention. The main EMBASE strategy for each search was independently peer reviewed by a second Information Specialist, using the Canadian Agency for Drugs and Technologies in Health (CADTH) Peer Review checklist.[40] Identified references were downloaded in EndNote X6 software (Thomson Reuters, CA, USA) for further assessment and handling. References in retrieved articles were checked for additional studies. The final list of included papers was also checked on PubMed for retractions, errata and related citations.[41–44]

The following databases were searched for relevant studies from database inception date to the most recent date available:

- MEDLINE (via Ovid): 1946 to March Week 3 2016
- MEDLINE In-Process & Other Non-Indexed Citations, and Daily Update (via Ovid): to 29 March 2016
- MEDLINE Epub Ahead of Print (via Ovid): 20 June 2016
- EMBASE (via Ovid): 1974 to 29 March 2016
- The Cochrane Library:
    - Cochrane Database of Systematic Reviews (CDSR) (via the internet): to Issue 3 of 12, March 2016
    - Cochrane Central Register of Controlled Trials (CENTRAL) (via the internet): to Issue 2 of 12, February 2016
    - Database of Abstracts of Reviews of Effects (DARE) (via the internet): to Issue 2 of 4, April 2015
    - Health Technology Assessment (HTA) database (via the internet): to Issue 1 of 4, January 2016
    - NHS Economic Evaluation Database (NHS EED) (via the internet): to Issue 2 of 4, April 2015
- International Network of Agencies for Health Technology Assessment (INAHTA) Publications (via the internet): to 30 March 2016: www.inahta.org/publications/
- National Institute for Health Research (NIHR) HTA programme (via the internet): to 30 March 2016

- Aggressive Research Intelligence Facility (ARIF) database (via the internet): to 30 March 2016: www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/index.aspx
- PROSPERO (International Prospective Register of Systematic Reviews) (via the internet): to 30 March 2016: www.crd.york.ac.uk/prospero/.

Completed and ongoing trials were identified by searches of the following resources:

- National Institutes of Health ClinicalTrials.gov: to 8 March 2016 www.clinicaltrials.gov/
- EU Clinical Trials Register: to 8 March 2016 www.clinicaltrialsregister.eu/ctr-search/search
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP): to 8 March 2016 www.who.int/ictrp/en/.

Electronic searches were undertaken for abstracts and poster presentations from the following conferences:

- American Gastroenterological Association – Digestive Disease Week (DDW): 2011–15
- Annual Meeting of the American Association for Clinical Chemistry and Laboratory Medicine (AACC): 2011–15
- British Society of Gastroenterology (BSG) Annual Meeting: 2011–15
- EuroMedLab: IFCC-EFLM (International Federation of Clinical Chemistry and Laboratory Medicine/ European Federation of Clinical Chemistry and Laboratory Medicine) European Congress of Clinical Chemistry and Laboratory Medicine: 2011–15
- United European Gastroenterology Week (UEGW): 2011–15.

Full search strategies are presented in *Appendix 1*.

Specialist members of the Assessment SubGroup and one additional clinical expert (CF) were contacted to seek additional studies.

Inclusion and exclusion criteria

Inclusion criteria for each of the clinical effectiveness questions are summarised in *Table 2*. Studies that fulfilled these criteria were eligible for inclusion in the review.

Inclusion screening and data extraction

Two reviewers (MW and SL) independently screened the titles and abstracts of all of the reports identified by searches and any discrepancies were discussed and resolved by consensus. Full copies of all of the studies that were deemed to be potentially relevant were obtained and the same two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus. Details of the studies excluded at the full-paper screening stage are presented in *Appendix 4*.

When studies reported insufficient information (e.g. FIT assay not specified or incomplete accuracy data), the authors were contacted to request additional information. The authors of studies that included a mixed population (e.g. screening, surveillance and symptomatic patients) were contacted to request subgroup data for symptomatic patients. Authors were initially contacted by e-mail, which was followed up with a reminder e-mail after 2 weeks and, subsequently (where possible), by personal contact from a clinical specialist member of the Assessment SubGroup (RL).

Studies cited in the materials provided by the manufacturers of FIT assays were first checked against the project reference database, in Endnote; any studies that were not already identified by our searches were screened for inclusion following the process described above.

TABLE 2 Inclusion criteria

Question	What is the accuracy of different quantitative FIT assays, when the target condition is CRC determined by colonoscopy (the reference standard method)?	What is the clinical effectiveness of faecal immunochemical testing, compared with guaiac faecal occult blood testing or no triage, for achieving appropriate referral for further investigation within the 2-week suspected cancer referral target?
Participants	People presenting with lower abdominal symptoms, who are being investigated for possible CRC[a]	
Setting	Primary care	
Interventions (index test)	Quantitative FIT assays listed in *Table 1*	
Comparators	Any other FIT method (including different faecal Hb cut-off points or different numbers of samples) or gFOBT or no comparator	gFOBT or no triage
Reference standard	Colonoscopy	NA
Outcomes	Diagnostic accuracy (the numbers of TP, FN, FP and TN test results), where the target condition is CRC determined by colonoscopy[b]	Appropriate referral for secondary care investigations with 2 weeks from presentation (proportion of patients referred for secondary care investigation in whom CRC was confirmed *and* proportion of patients not referred for secondary care investigation in whom CRC was later diagnosed[c]), long-term CRC mortality,[d] any patient acceptability/satisfaction or HRQoL measures
Study design	Diagnostic cohort studies	RCTs (CCTs will be considered if no RCTs are identified)

CCT, controlled clinical trial; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; NA, not applicable; RCT, randomised controlled trial; TN, true negative; TP, true positive.

a Studies will be included if the participant selection criteria are unclear but the population is described as symptomatic/suspected CRC and *not* asymptomatic population-based screening; study authors will be contacted for additional details as needed. Studies conducted in people with pre-existing GI comorbidities will be excluded.

b If studies report diagnostic accuracy data for other target conditions, in addition to CRC (e.g. adenoma, IBD, organic bowel disease) then these data will also be extracted. Any reported data on test failure rates or measures of patient acceptability/satisfaction will also be extracted.

c Patients who are not referred for secondary care investigation should be followed up for a minimum of 1 year.

d Studies reporting CRC mortality should have a minimum follow-up of 5 years.

Data were extracted on the following: study details, inclusion and exclusion criteria, participant characteristics (demographic characteristics, presenting symptoms, other CRC risk factors), target condition {CRC, advanced neoplasia [high-risk adenoma (HRA) or CRC], other significant bowel disease outcomes (as reported)}, details of the FIT (manufacturer, analyser used, definition of a cut-off point, sampling procedure, detection method, etc.), details of any comparator test(s) (manufacturer, antibody, limit of quantitation, definition of cut-off point, sampling procedure, detection method, etc.), details of the reference standard, definitions of the target conditions, test performance outcome measures [numbers of true-positive (TP), FP, FN and true-negative (TN) test results] and proportion of study participants who returned a FIT sample (extracted as an indicator of acceptability). Data were extracted by one reviewer, using a piloted, standard data extraction form and checked by a second reviewer (MW and SL); any disagreements were resolved by consensus. Full data extraction tables are provided in *Appendix 2*.

Quality assessment

The methodological quality of included studies was assessed using QUADAS-2.[45]

Note: *Protocol change* Studies that reported results for risk prediction scores that included faecal immunochemical testing, as well as test accuracy data for faecal immunochemical testing, were assessed using PROBAST (Prediction model study Risk Of Bias Assessment Tool)[46] in addition to QUADAS-2.

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

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

Methods of analysis/synthesis

Sensitivity and specificity were calculated for each set of 2 × 2 data. The bivariate/hierarchical summary receiver operating characteristic (HSROC) model was used to estimate summary sensitivity and specificity with 95% CIs and prediction regions around the summary points, and to derive HSROC curves for meta-analyses involving four or more studies.[47–49] This approach allows for between-study heterogeneity in sensitivity and specificity, and for the trade-off (negative correlation) between sensitivity and specificity that is commonly seen in diagnostic meta-analyses. For meta-analyses with fewer than four studies we estimated separate pooled estimates of sensitivity and specificity, using random-effects logistic regression.[50] Heterogeneity was assessed visually using summary receiver operating characteristic (SROC) plots and statistically using the variance of logit (sensitivity) and logit (specificity), for which 'logit' indicates the logistic function: the smaller these values, the less heterogeneity between studies. Analyses were performed in Stata 10 (StataCorp LP, College Station, TX, USA), using the *metandi* command. For analyses that would not run in Stata we used Meta-DiSc (version 1.4, free source).[51]

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

We used SROC plots to display summary estimates from analyses that included a minimum of four data points.

Results of the assessment of clinical effectiveness assessment

After initial screening of titles and abstracts, 113 papers were considered to be potentially relevant and ordered for full-paper screening; of these, 21 papers[13,52–71] were included in the review.

Additionally, four presentations[72–75] were obtained through contact with a clinical expert (CF). One unpublished manuscript was provided, through NICE, by the manufacturer of FOB Gold [e-mail from Philippa Pinn, Sysmex UK Ltd, via Rebecca Albrow, NICE, to Marie Westwood, Kleijnen Systematic Reviews (KSR) Ltd, 21 June 2016, personal communication]. Additional unpublished work was provided by the clinical expert (CF) (e-mail from Callum Fraser, NHS Tayside, to Marie Westwood, KSR Ltd, 10 July 2016, personal communication, ahead of publication). All potentially relevant studies cited in other documents supplied by the test manufacturers had already been identified through other sources. *Figure 1* shows the flow of studies through the review process, and *Appendix 4* provides details, with reasons for exclusions, of all of the publications that were excluded at the full-paper screening stage. In total there were 10 included studies derived from 27 articles.

Seventy-four articles were excluded after full-text screening. Twelve articles[76–86] could not be obtained and one further article[87] was published in Russian with no English abstract.

We contacted the authors of publications that reported data from studies with mixed populations (symptomatic, screening and surveillance patients) to request separate data for the symptomatic subgroup; when no additional data were obtained, these studies were excluded (see *Appendix 4*). The authors of two studies[56,58] provided additional test accuracy data, which were included in our review.

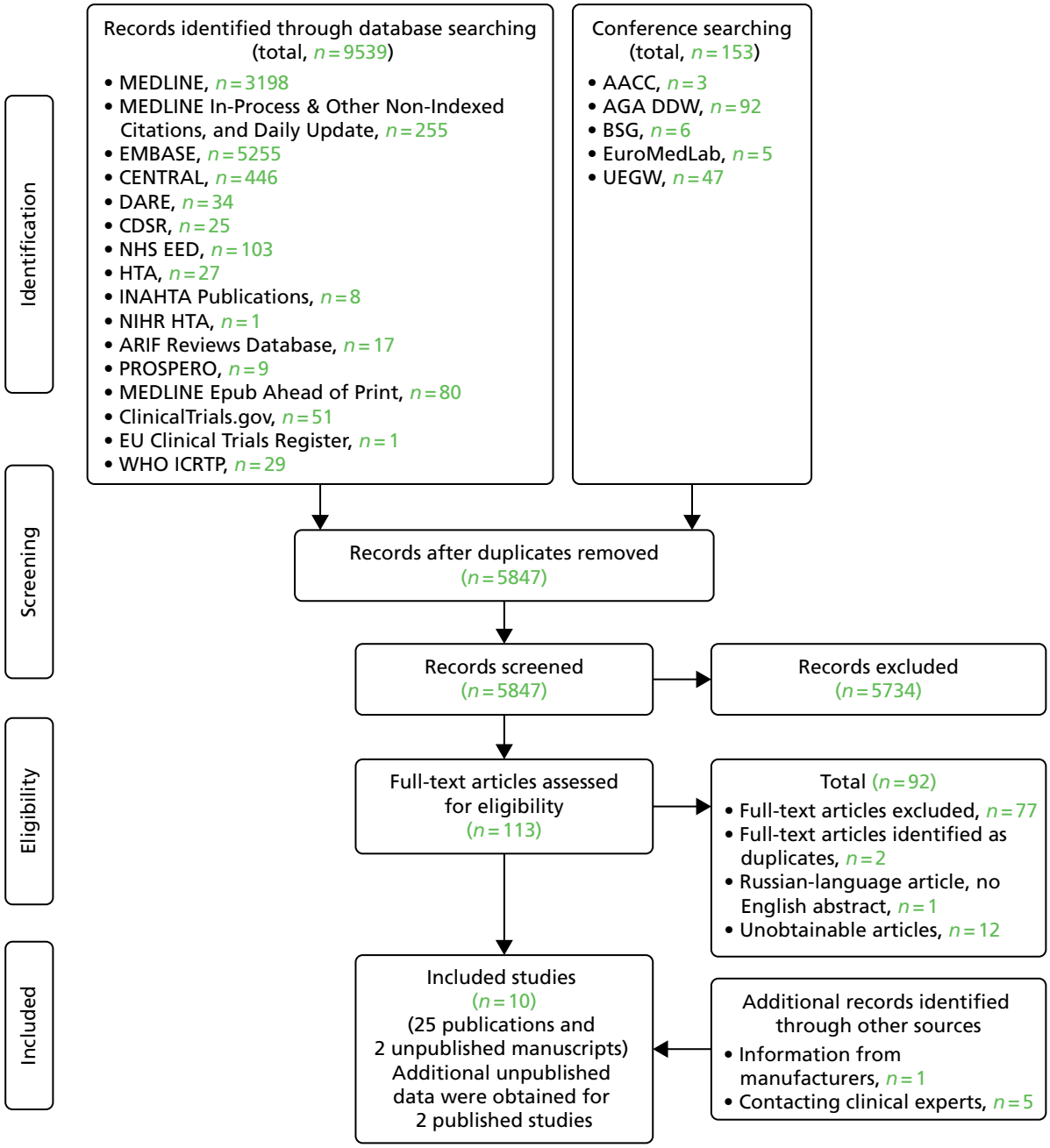

FIGURE 1 Flow of studies through the review process. AGA DDW, American Gastroenterological Association Digestive Disease week; UEGW, United European Gastroenterology Federation Week.

Overview of included studies

Details of the 10 included studies and their associated references are provided in *Table 3*. Additional data were supplied by the authors of two studies.[56,58] In the case of Terhaar sive Droste *et al.*,[58] the authors provided overall data for symptomatic study from the master database, which holds data for all of their publications (e-mail from Sietze van Turenhout, University Medical Center, Amsterdam, to Marie Westwood, KSR Ltd, 12 June 2016, personal communication). The results section of this report cites studies using the primary publication and, where this is different, the publication (shown in bold text in *Table 3*) in which the referenced data were reported.

TABLE 3 Details of included studies

Details	Country	*n*	Reference standard
HM-JACKarc			
Thomas 2016[75]	England	450	CT/colonoscopy
Godber 2016[56]	Scotland	484	Colonoscopy
Macdonald 2015[71]			
Godber 2014[65]			
Auge 2016[57]	Spain	208	Colonoscopy
Auge 2014[66]			
Auge 2015[72]			
FOB Gold system			
Krivec 2011[54]	Slovenia	NR	Colonoscopy
(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
OC-Sensor			
McDonald 2012[13]	Scotland	280	Colonoscopy and flexible sigmoidoscopy
Mowat 2015[52]	Scotland	755	Colonoscopy
Steele 2014[74]			
Rodríguez-Alonso 2015[53]	Spain	1003	Colonoscopy
Cubiella 2014 (COLONPREDICT)[55]	Spain	787	Colonoscopy
Diaz Ondina 2014[61]			
Cubiella 2015[73]			
Unpublished data[a]			
Terhaar sive Droste 2011[58]	The Netherlands	2058	Colonoscopy
Oort 2011[63]			
van Turenhout 2010[69]			
van Turenhout 2014[59]			
van Turenhout 2012[62]			
van Turenhout 2011[68]			
Oort 2010[64]			
van Turenhout 2012[60]			
Larbi 2012[67]			
van Turenhout 2010[70]			

CT, computed tomography; NR, not reported.
a E-mail from Callum Fraser, personal communication.

Five studies[2,13,53,55,58] reported accuracy data for the OC-Sensor assay; one study[52] used the IO analyser (Eiken Chemical Co.), one study[13] used the OC-Sensor Diana automated immunoturbidimetric analyser (Eiken Chemical Co.), two studies[53,58] used the MICRO desktop analyser (Eiken Chemical Co.) and one study[55] did not report the analyser used. Three studies[56,57,75] reported accuracy data for the HM-JACKarc automated system (Kyowa Medex, Tokyo, Japan). The remaining two studies reported accuracy data for the FOB Gold assay; one used the Roche Modular P/917 analyser (Roche Diagnostics Ltd, West Sussex, UK),[54] and the other used the SENTiFIT 270 analyser (Sentinel Diagnostics, Milan, Italy) (Philippa Pinn, personal

communication). There were no studies, using the RIDASCREEN Hb or the RIDASCREEN Hb/Hp complex assays, which met the inclusion criteria for this assessment. None of the included studies reported data comparing different FIT assays, or comparing one or more FIT assays with a gFOBT method. All of the studies included in our systematic review were diagnostic cohort studies that reported data on the diagnostic accuracy of faecal immunochemical testing for which the target condition was CRC or advanced neoplasia (defined as CRC or HRA). Five studies[13,52,56,58,75] reported additional accuracy data for various non-malignant and composite target conditions.

Six of the diagnostic accuracy studies[13,52,53,55,56,75] included in our systematic review also reported uptake rates for participants who were invited to provide a sample for faecal immunochemical testing.

No randomised controlled trials (RCTs) or controlled clinical trials (CCTs) were identified; no studies provided data on patient-relevant outcomes following faecal immunochemical testing compared with guaiac faecal occult blood testing or no faecal occult blood testing.

All 10 of the included studies[2,13,52–58,75] were conducted in Europe: one in England,[75] three in Scotland,[13,52,56] three published studies[53,55,57] and one unpublished study (Philippa Pinn, personal communication) in Spain, and one each in the Netherlands[58] and Slovenia.[54] Three studies[52,53,55] were publicly funded, five studies[13,55–57,75] reported receiving some funding from manufacturers (including supply of test kits, reagents and analysers), one study[54] did not report details of funding and the unpublished study was conducted at the request of the test manufacturer.

Full details of the characteristics of study participants, study inclusion and exclusion criteria, and FIT assay used and reference standard are reported in the data extraction tables presented in *Appendix 2* (see *Tables 65* and *66*).

Study quality

All studies included in this systematic review were diagnostic cohort studies. The methodological quality of these studies was assessed using the QUADAS-2 tool[45] (summarised in *Table 4* and *Figure 2*). One of these studies[53] and an additional report[73] and unpublished paper (Callum Fraser, personal communication) linked to a second study[55] reported the development and validation of risk prediction scores that included faecal immunochemical testing, in addition to test accuracy results. These studies were assessed using PROBAST (*Table 5*), as well as QUADAS-2. The full QUADAS-2 assessments for each study are provided in *Appendix 3a* and PROBAST assessment results are provided in *Appendix 3b*.

Two studies[54,75] were reported only as conference abstracts, with limited descriptions of methods.

Two studies[55,57] were rated as 'low' risk of bias for all domains. (Confidential information has been removed.) The main potential sources of bias, across the included studies, concerned flow and timing, and application of the index test. Three studies[13,52,75] were rated as 'high' risk of bias on the flow and timing domain because some patients who returned a sample for faecal immunochemical testing or who agreed to participate in the study were subsequently excluded from the analysis: Mowat *et al.* 2015[52] excluded 11% of participants who returned a FIT sample because they were not subsequently referred to secondary care or because the referral was cancelled; Thomas *et al.* 2016[75] excluded 12.5% of participants who returned a FIT sample (no reasons for exclusion were reported); McDonald *et al.* 2012[13] excluded 41% of people who originally agreed to participate in the study (38% did not return a FIT sample before endoscopy and 3% completed faecal immunochemical testing but not endoscopy). (Confidential information has been removed.)

All of the included studies were rated as having 'high' concerns about applicability with respect to participants. This was because no study reported data that were specific to the population that was defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC according to the criteria defined in NG12[1]). Only one study[52]

TABLE 4 The QUADAS-2 results for studies of FIT assays

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient	Index test	Reference standard
Auge 2016[57]	+	+	+	+	–	+	+
Cubiella 2014 (COLONPREDICT)[55]	+	+	+	+	–	+	+
Godber 2016[56]	+	+	?	+	–	+	+
(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Krivec 2011[54]	?	–	?	?	–	+	–
McDonald 2012[13]	+	+	?	–	–	+	?
Mowat 2015[52]	+	+	+	–	–	+	+
Rodríguez-Alonso 2015[53]	?	+	+	+	–	+	+
Terhaar sive Droste 2011[58]	+	+	+	?	–	+	+
Thomas 2016[75]	?	+	?	–	–	+	+

+, low risk; –, high risk; ?, unclear risk.
(Confidential information has been removed.)

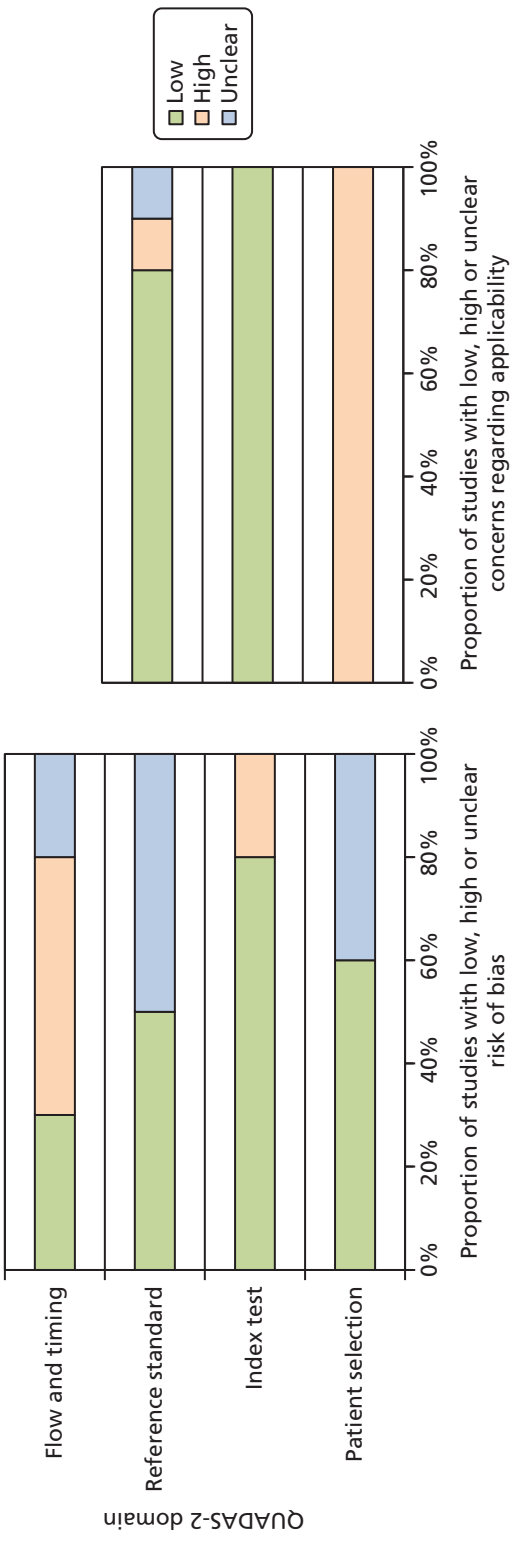

FIGURE 2 Summary of QUADAS-2 results for studies of FIT assays.

TABLE 5 The PROBAST results for studies reporting the development and validation of risk scores that included faecal immunochemical testing

Study	Risk of bias										
	Participant selection		Predictors		Outcome		Sample size and participant flow		Analysis		Overall judgement
	Development	Validation	Development	Validation	Development	Validation	Development	Validation	Development	Validation	
[a]Cubiella 2015 (COLONPREDICT)[73]	+	+	–	–	+	–	?	?	?	?	–
Rodríguez-Alonso 2015[53]	+	+	?	?	+	+	?	?	–	–	–

FAST, Faecal haemoglobin, Age and Sex Test.
a Based on a draft of the full paper reporting the development and validation of a risk score, the FAST score has been provided in confidence (Callum Fraser, personal communication).
+, low risk; –, high risk; ?, unclear risk.

TABLE 5 The PROBAST results for studies reporting the development and validation of risk scores that included faecal immunochemical testing (*continued*)

Study	Applicability concerns						
	Participant selection		Predictors		Outcome		Overall judgement
	Development	Validation	Development	Validation	Development	Validation	
[a]Cubiella 2015 (COLONPREDICT)[73]	–	–	–	–	+	+	–
Rodríguez-Alonso 2015[53]	–	–	–	–	+	+	–

was conducted in a primary care setting, reporting that faecal immunochemical testing was ordered by GPs at the point of referral to secondary care. All of the studies included some participants who had symptoms that may be considered to be associated with a higher probability of CRC, and which are components of the criteria for 2-week referral as defined in NG12[1] (e.g. rectal bleeding). In addition, although all of the included studies were conducted in Europe, only four studies[13,52,56,75] were conducted in the UK (one in England[75] and three in Scotland[13,52,56]). Given that population studies have shown variation in faecal Hb concentrations, and hence potential variation in optimal thresholds for faecal immunochemical testing across different geographic location,[88,89] this may limit the applicability of our findings to UK settings.

Diagnostic performance of the OC-Sensor faecal immunochemical test assay

Details of OC-Sensor studies

Five diagnostic cohort studies,[13,52,53,55,58] reported in 17 publications,[13,52,53,55,58–64,67–70,73,74] provided data on the diagnostic performance of the OC-Sensor FIT assay. All five studies[13,52,53,55,58] reported accuracy data, for which CRC was the specified target condition,[13,52,53,55,58] and one of these studies[55] reported further information about the sensitivity of faecal immunochemical testing for differentiating CRC stage and location. The prevalence of CRC, diagnosed at colonoscopy, was 2.1% in the McDonald *et al.* study,[13] 3.0% in the Rodríguez-Alonso *et al.* study,[53] 3.7% in the Mowat *et al.* study,[52] 5.4% in the symptomatic subgroup from Terhaar sive Droste *et al.* study[58] and 12.3% in the Cubiella *et al.* study.[55] Four studies[13,52,53,55] also reported data for the composite target condition of advanced neoplasia (CRC or HRA); where a definition was provided, HRA was defined as adenoma $\geq$ 10 mm in diameter, with villous architecture or high-grade dysplasia.[53,55] Three studies reported additional accuracy data various non-malignant and composite target conditions.[13,52,58]

No study reported data that were specific to the population that was defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC according to the criteria defined in NG12[1]). Only one study[52] was conducted in a primary care setting, reporting that faecal immunochemical testing was ordered by GPs at the point of referral to secondary care. In another study,[53] faecal immunochemical testing was ordered either by GPs at the point of referral or at the initial secondary care appointment. Two studies reported that faecal immunochemical testing was requested after referral to secondary care and before colonoscopy[13,55] but did not report whether the test was requested by GPs or secondary care clinicians. The remaining study stated that patients already scheduled for colonoscopy were asked to provide a sample for faecal immunochemical testing before bowel preparation.[58] Four[52,53,55,58] of the five OC-Sensor studies[13,52,53,55,58] explicitly reported that they included only symptomatic participants and provided details of the presenting symptoms, and the remaining study[13] included patients referred for colonoscopy (no screening colonoscopies included). However, all of the studies included some participants who had symptoms that may be considered to be associated with a higher probability of CRC and that are components of the criteria for 2-week referral as defined in NG12[1] (e.g. rectal bleeding). Presenting symptoms included altered bowel habit, rectal bleeding, diarrhoea, constipation, abdominal pain, bloating, unspecified anaemia, iron-deficiency anaemia, weight loss and palpable mass. Where reported, the median age of study participants was 64 years,[52] 67 years[55] and 60 years,[58] and the overall age range was 16–91 years. There were no data linking presenting symptoms to age or sex. Full details of participant characteristics are provided in *Appendix 2*, *Table 65*.

All five studies[13,52,53,55,58] reported data on the accuracy of OC-Sensor faecal immunochemical testing using a single faecal sample. No data were available on the effects of multiple sampling on test performance in symptomatic patients; one additional publication,[63] associated with Terhaar sive Droste *et al.*,[58] reported no difference between various double sampling strategies and single sampling. However, this study was conducted in a mixed population and additional subgroup data provided by the authors were only for single sampling.

Four studies[13,52,53,55] reported information about uptake rates in participants invited to provide a sample for faecal immunochemical testing.

Accuracy of OC-Sensor for the detection of colorectal cancer

Five studies[13,52,53,55,58] reported data on the accuracy of OC-Sensor FIT using a single faecal sample, and thresholds ranging from any detectable Hb (the limit of detection for the assay is 4[52,53] to 40[58] µg Hb/g faeces). Full test performance results for all thresholds evaluated in individual studies and summary estimates, where these were calculated, are provided in *Table 6*. The variation in test performance characteristics according to the threshold used is illustrated in a ROC space plot (*Figure 3*). Although test performance did not vary greatly with threshold, as might be expected, sensitivity estimates generally decreased and specificity estimates increased with increasing threshold. Specificity was low (< 50%) in both of the studies that used any detectable Hb to define a positive test.[52,53]

The optimal test performance (maximising both sensitivity and specificity) appeared to occur with thresholds of 10 or 15 µg Hb/g faeces, with most data being available for the 10 µg Hb/g faeces threshold. The summary estimates of sensitivity and specificity, using the 10 µg Hb/g faeces threshold, were 92.1% (95% CI 86.9% to 95.3%) and 85.8% (95% CI 78.3% to 91.0%), respectively, based on data from four studies,[13,52,53,58] (see *Table 6* and *Figure 4*). Mowat *et al.*[52] and Rodríguez-Alonso *et al.*[53] reported data for both the 10 µg Hb/g faeces threshold and the minimum threshold of any detectable Hb; the prevalence of CRC in these two studies[52,53] was 3.3%. Using test performance data from these two studies,[52,53] and a CRC prevalence estimate of 3.3%, to consider the outcome of testing for a hypothetical cohort of 1000 patients indicates that two CRCs would be missed using the 10 µg Hb/g faeces threshold and 198 unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and all of the colonoscopies that are conducted in patients without CRC are considered unnecessary); CRC would be correctly ruled out by faecal immunochemical testing, avoiding colonoscopy, in 769 people (*Figure 5a*). Alternatively, using a very low threshold (any detectable Hb) would result in no CRCs being missed, but would increase the number of 'unnecessary' colonoscopies to 548 and reduce the number of people in whom CRC would be correctly ruled out to 419 (*Figure 5b*). Please see subsequent sections for information on other significant bowel pathologies that may be detected by faecal immunochemical testing and hence may form part of the FP or 'unnecessary colonoscopy' population.

Limited data from Cubiella *et al.*[55] indicated that the sensitivity of OC-Sensor (using a threshold of 20 µg Hb/g faeces) is higher for more advanced stages of CRC [American Joint Committee on Cancer (AJCC) stages II–IV] and is also higher for tumours of the distal colon than for tumours of the proximal colon or rectum (*Table 7*).

Accuracy of OC-Sensor for the detection of advanced neoplasia (colorectal cancer or high-risk adenoma)

Four of the studies described in the previous section also reported data on the accuracy of OC-Sensor FIT using a single faecal sample, where the target condition was expanded to include CRC or HRA.[13,52,53,55] The thresholds assessed ranged from any detectable Hb (the limit of detection for the assay is 4 µg Hb/g faeces)[52,53] to 20 µg Hb/g faeces.[53] Full test performance results for all thresholds evaluated in individual studies and summary estimates, where they were calculated, are provided in *Table 8*. The variation in test performance characteristics according to the threshold used is illustrated in a ROC space plot (*Figure 6*).

For this expanded target condition, sensitivity estimates were low for all thresholds except any detectable Hb; the summary sensitivity and specificity estimates for this threshold were 84.1% (95% CI 78.3% to 88.8%) and 45.2% (95% CI 42.7% to 47.7%), respectively, based on data from the same two studies[52,53] that evaluated this threshold for the detection of CRC.

Expanding the target condition from CRC only, to include CRC or HRA, resulted in an increase in prevalence from 3.3% to 11.5%.[52,53] Using test performance data from these two studies,[52,53] and an estimate for the prevalence of advanced neoplasia of 11.5%, to consider the outcome of testing for a

TABLE 6 Accuracy of OC-Sensor for the detection of CRC using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable Hb									
Mowat 2015[52]	0[a]	28	0	409	313	750	Reported	100 (87.7 to 100)[b]	43.4 (39.7 to 47.1)[b]
Rodríguez-Alonso 2015[53]	0[a]	30	0	552	421	1003	Calculated	100 (88.4 to100)	43.3 (40.1 to 46.4)
Summary estimate								**100 (93.8 to 100)**	**43.3 (40.9 to 45.7)**
10 µg Hb/g faeces or equivalent									
McDonald 2012[13]	≥ 10[c]	6	0	17	257	280	Calculated	100 (54.1 to 100)	93.8 (90.3 to 96.3)
Mowat 2015[52]	≥ 10	25	3	151	571	750	Reported	89.3 (71.8 to 97.7)[b]	79.1 (75.9 to 82)[b]
Rodríguez-Alonso 2015[53]	≥ 10	29	1	196	777	1003	Calculated	96.7 (82.8 to 99.9)	79.9 (77.2 to 82.3)
[d]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Summary estimate								**92.1 (86.9 to 95.3)**	**85.8 (78.3 to 91.0)**
15 µg Hb/g faeces or equivalent									
Rodríguez-Alonso 2015[53]	≥ 15	29	1	164	809	1003	Calculated	96.7 (82.8 to 99.9)	83.1 (80.6 to 85.4)
[d]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Summary estimate								**92.3 (86.6 to 96.1)**	**86.9 (85.6 to 88.1)**

continued

TABLE 6 Accuracy of OC-Sensor for the detection of CRC using a single faecal sample (*continued*)

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
20 µg Hb/g faeces or equivalent									
Cubiella 2014 (COLONPREDICT)[55]	≥ 20[c]	85	12	156	534	787	Calculated	87.6 (79.0 to 93.2)	77.4 (74.0 to 80.4)
Rodríguez-Alonso 2015[53]	≥ 20	28	2	135	838	1003	Calculated	93.3 (77.9 to 99.2)	86.1 (83.8 to 88.2)
[d]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Summary estimate								**89.5 (84.9 to 93.1)**	**86.6 (85.4 to 87.7)**
Other thresholds									
[d]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
[d]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

The results of meta-analyses (Summary estimate) are reported in bold.
a The limit of detection for the assay is 4 µg Hb/g faeces or 20 ng/ml buffer.
b Calculated estimate.
c Converted from 'ng Hb/ml buffer' using a multiplication factor of 0.2.[17,18]
d Sietze van Turenhout, personal communication; unpublished data provided in confidence.

FIGURE 3 (Confidential information has been removed.)

FIGURE 4 (Confidential information has been removed.)

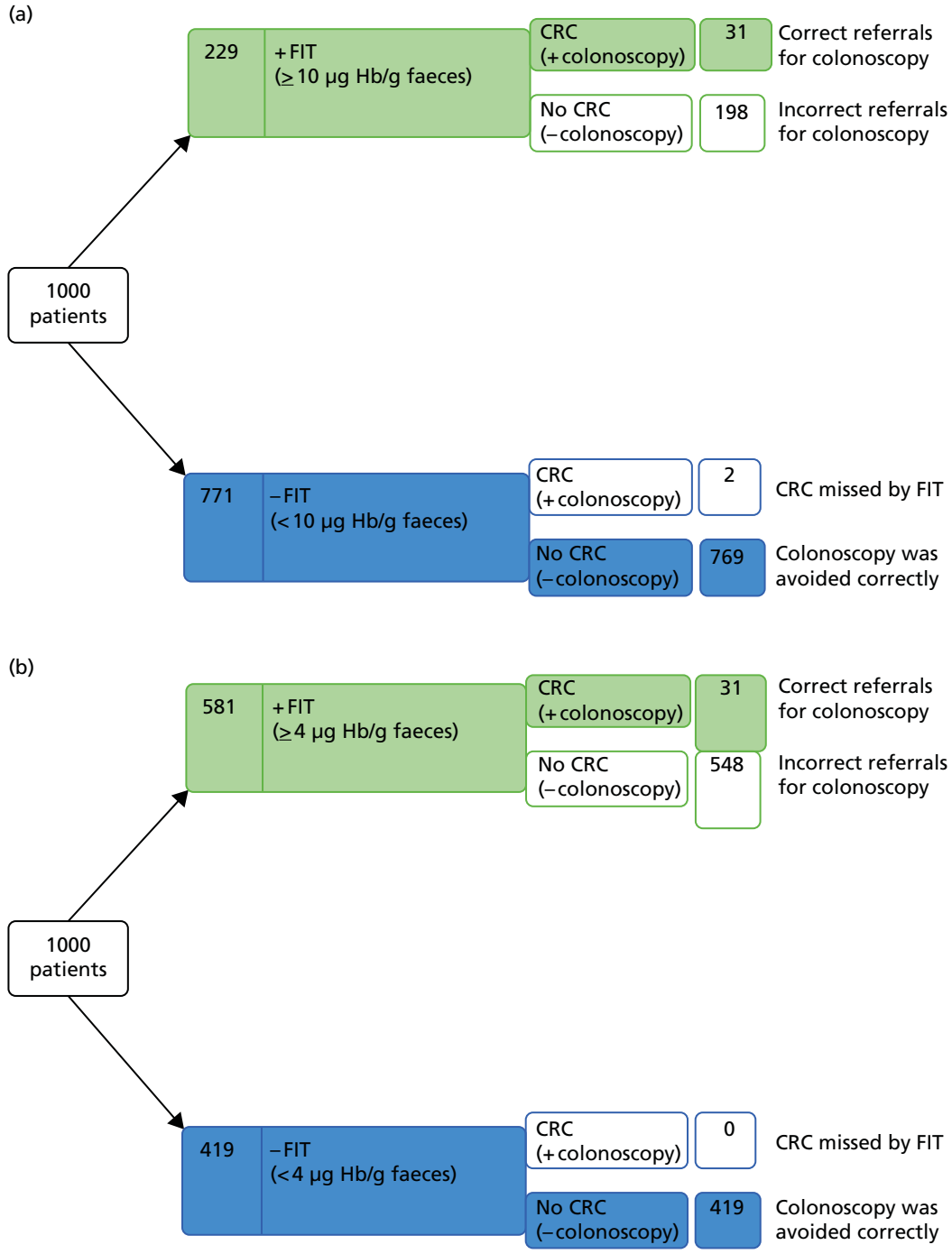

FIGURE 5 Testing outcomes for a hypothetical cohort of 1000 patients using OC-Sensor at (a) the 10 µg Hb/g faeces threshold; and (b) any detectable Hb, for the target condition CRC.

TABLE 7 Sensitivity of OC-Sensor for determining the stage and location of CRC using a single faecal sample

Study	Target condition	Subgroup	Threshold (µg Hb/g faeces)	TP	FN	Total *n*	Sensitivity % (95% CI)
CRC location							
Cubiella 2014 (COLONPREDICT)[55]	Rectum	Participants with CRC	≥ 20[a]	26	4	30	86.7 (69.3 to 96.2)
	Distal colon	Participants with CRC	≥ 20[a]	40	4	44	90.9 (78.3 to 97.5)
	Proximal colon	Participants with CRC	≥ 20[a]	19	4	23	82.6 (61.2 to 95.0)
CRC stage (AJCC classification)							
Cubiella 2014 (COLONPREDICT)[55]	0	Participants with CRC	≥ 20[a]	4	1	5	80 (28.4 to 99.5)
	I	Participants with CRC	≥ 20[a]	12	3	15	80 (51.9 to 95.7)
	II	Participants with CRC	≥ 20[a]	21	2	23	91.3 (72.0 to 98.9)
	III	Participants with CRC	≥ 20[a]	35	5	40	87.5 (73.2 to 95.8)
	IV	Participants with CRC	≥ 20[a]	12	1	13	92.3 (64.0 to 99.8)

a Converted from 'ng Hb/ml buffer' using a multiplication factor of 0.2.[17,18]

hypothetical cohort of 1000 patients indicates that 18 advanced neoplasias would be missed, even when using the minimum threshold of any detectable Hb. As data indicate that no CRCs would be missed at this threshold (see previous section), it may be assumed that the missed cases would all be HRAs. Using the any detectable Hb threshold, 485 unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and all of the colonoscopies that are conducted in patients without at least HRA are considered unnecessary); CRC and HRA would be correctly ruled out in 401 people (*Figure 7a*). If the 10 µg Hb/g faeces threshold were applied to the expanded target condition, for hypothetical cohort of 1000 patients, the number of missed cases would increase from 2 to 42 (two CRCs and 40 HRAs); using this threshold, 157 unnecessary colonoscopies would be carried out and CRC and HRA would be correctly ruled out in 729 people (*Figure 7b*).

Accuracy of OC-Sensor for the detection of other/composite target conditions

Three studies[13,52,58] reported accuracy data for target conditions other than CRC or advanced neoplasia (CRC or HRA).

McDonald *et al.*[13] evaluated the diagnostic performance of OC-Sensor (10 µg Hb/g faeces threshold) for two composite target conditions: one including CRC and all adenomas and the other including CRC and all adenomas plus inflammatory bowel disease (IBD). The sensitivity estimates were low for both composite target conditions, 58.3% (95% CI 44.9% to 70.9%) and 57.0% (95% CI 45.8% to 67.6%), respectively, and the corresponding specificity estimates were high, 98.6% (95% CI 96.1% to 99.7%) and 99.0% (95% CI 96.3% to 99.9%). Mowat *et al.*[52] reported similar test performance characteristics for the 10 µg Hb/g faeces threshold and a composite target condition that included CRC, HRA or IBD; the reported sensitivity was 68.6% (95% CI 58.7% to 77.5%) and the specificity was 83.6% (95% CI 80.6% to 86.4%). It should be noted that an important consequence of this increased specificity estimate, relative to that reported for the target condition of CRC in the same cohort of patients, is that 45 of the 151 participants

TABLE 8 Accuracy of OC-Sensor for the detection of advanced neoplasia (CRC or HRA) using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable Hb									
Mowat 2015[52]	0[a]	61	7	376	306	750	Calculated	89.7 (79.9 to 95.8)[b]	44.9 (41.1 to 48.7)[b]
Rodríguez-Alonso 2015[53]	0[a]	108	25	474	396	1003		81.2 (73.5 to 87.5)	45.5 (42.2 to 48.9)
Summary estimate								**84.1 (78.3 to 88.8)**	**45.2 (42.7 to 47.7)**
10 µg Hb/g faeces									
McDonald 2012[13]	≥ 10[c]	17	12	6	245	280	Calculated	58.6 (38.9 to 76.5)	97.6 (94.9 to 99.1)
Mowat 2015[52]	≥ 10	45	23	131	551	750		66.2 (53.7 to 77.2)[b]	80.8 (77.6 to 83.7)[b]
Rodríguez-Alonso 2015[53]	≥ 10	82	51	144	726	1003		61.7 (52.8 to 69.9)	83.4 (80.8 to 85.9)
Summary estimate								**62.6 (56.0 to 68.9)**	**84.4 (82.7 to 86.1)**
20 µg Hb/g faeces or equivalent									
Cubiella 2014 (COLONPREDICT)[55]	≥ 20[c]	127	50	114	496	787	Calculated	71.8 (64.4 to 78.1)	81.3 (77.9 to 84.3)
Rodríguez-Alonso 2015[53]	≥ 20	71	62	92	778	1003		53.4 (44.5 to 62.1)	89.4 (87.2 to 91.4)
Summary estimate								**63.9 (58.2 to 69.2)**	**86.1 (84.2 to 87.8)**
Other thresholds									
Rodríguez-Alonso 2015[53]	≥ 15	76	57	117	753	1003	Calculated	57.1 (48.3 to 65.7)	86.6 (84.1 to 88.7)

a The limit of detection for the assay is 4 µg Hb/g faeces or 20 ng/ml buffer.
b Calculated estimate.
c Converted from 'ng Hb/ml buffer' using a multiplication factor of 0.2.[17,18]

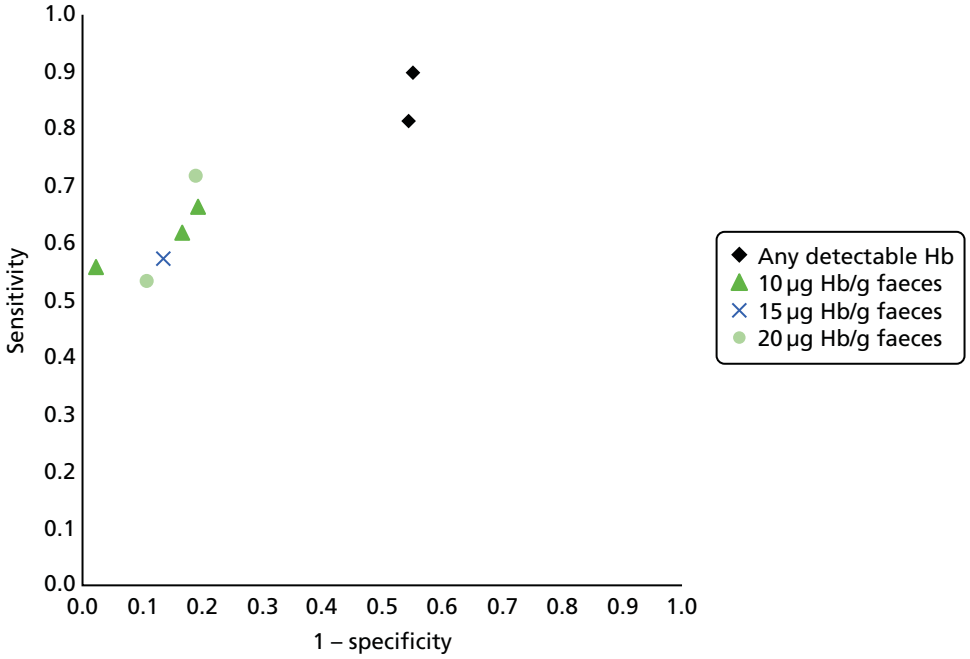

FIGURE 6 Receiver operating characteristic space plot for the OC-Sensor assay using different thresholds for the target condition of advanced neoplasia (CRC or HRA).

(29.8%) who were classified as having FP FIT results for CRC actually had other significant bowel pathologies (HRA or IBD) and may thus have benefited from secondary care investigation.[52] Mowat *et al.*[52] also reported test performance data for this composite target condition, using the minimum threshold of any detectable Hb. This lowering of the threshold resulted in an increased estimate of sensitivity, 88.2% (95% CI 80.4% to 93.8%), and lower specificity, 46.5% (95% CI 42.6% to 50.4%).[52]

Mowat *et al.*[52] reported separate test performance estimates for the individual target conditions of HRA and IBD. However, these estimates are likely to be of limited clinical relevance, as they appear to have been calculated by classifying any patient who was not in the specified target condition category as disease negative: for HRA estimates, patients with CRC (as well as those with low-risk adenoma IBD or no significant findings) were classified as disease negative; for IBD, patients with CRC or HRA (as well as those with no significant findings) were classified as disease negative. One further study[58] calculated test performance estimates for HRA using a range of thresholds from 10 to 40 µg Hb/g faeces; patients with CRC were excluded from these analyses. Full test performance results for all of the thresholds and target conditions that were evaluated in individual studies are provided in *Table 9*.

Acceptability of faecal immunochemical testing using OC-Sensor

The proportion of people who are invited to participate in faecal immunochemical testing and who return a faecal sample can be regarded as a possible indicator of the acceptability of faecal immunochemical testing. Four[13,52,53,55] of the five OC-Sensor studies reported faecal immunochemical testing uptake rates and these varied widely, ranging from 41% (in a study for which patients were sent an invitation to participate along with their referral letter)[13] to 98% (in a study for which patients were given the specimen collection device at their initial consultation with a gastroenterologist).[53] Full results are provided in *Table 10*.

Other outcome measures for faecal immunochemical testing using OC-Sensor

The primary care study by Mowat *et al.*[52] reported a number of additional outcomes relating to referral pathways for patients receiving faecal immunochemical testing. This study found that 11% (114/1031) of patients for whom a FIT sample was analysed were subsequently not referred to secondary care.[13] The study[13] also reported that 69% (715/1031) of patients for whom a FIT sample was analysed were referred

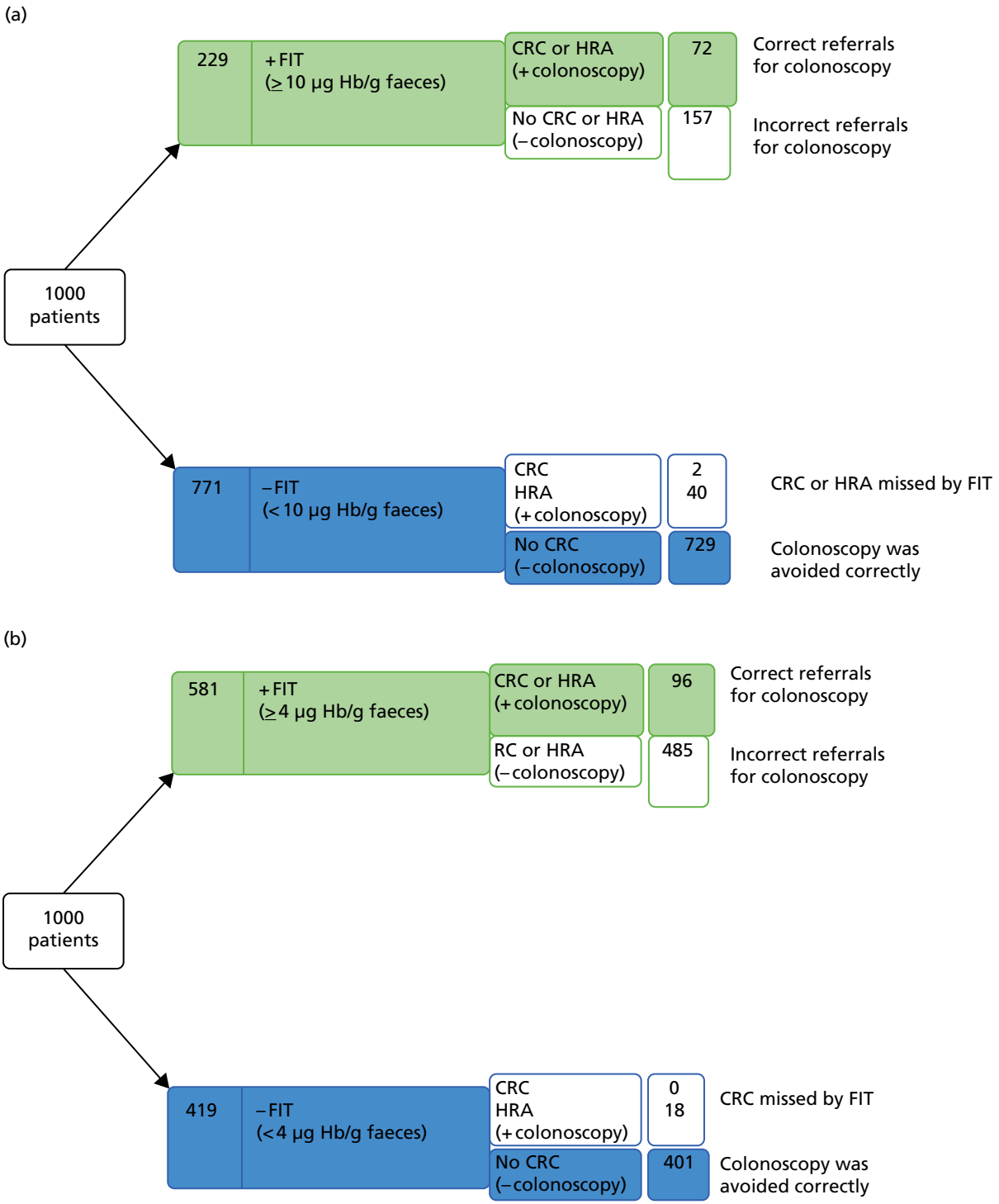

FIGURE 7 Testing outcomes for a hypothetical cohort of 1000 patients using OC-Sensor at (a) any detectable Hb, for the target condition of advanced neoplasia (CRC or HRA); and (b) the 10 µg Hb/g faeces threshold.

straight to endoscopy and 20% (202/1031) were referred to an outpatient clinic; however, decisions about the urgency of the referral appear to have been made prior to faecal immunochemical testing.

The Mowat *et al.* study[52] was also the only OC-Sensor study to report information about the proportion of returned samples that were considered to be unsuitable for FIT analysis; this was found to be < 1% (7/1043).[13]

TABLE 9 Accuracy of OC-Sensor for the detection of other/composite target conditions using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
All neoplasia (CRC, HRA or low-risk adenoma)									
McDonald 2012[13]	≥ 10[a]	35	25	3	217	280	Calculated	58.3 (44.9 to 70.9)	98.6 (96.1 to 99.7)
HRA									
Mowat 2015[52]	0[b]	33	7	404	306	750[c]	Reported	82.5 (67.2 to 92.7)[d]	43.1 (39.4 to 46.8)[d]
Mowat 2015[52]	≥ 10	20	20	156	554	750[c]		50.0 (33.8 to 66.2)[d]	78.0 (74.8 to 81.0)[d]
[e,f]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
[e,f]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
[e,f]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
[e,f]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
[e,f]Terhaar sive Droste 2011[58]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
IBD									
Mowat 2015[52]	0[b]	29	5	408	308	750[g]	Reported	85.3 (68.9 to 95.0)[d]	43.0 (39.4 to 46.7)[d]
Mowat 2015[52]	≥ 10	25	9	151	565	750[g]		73.5 (55.6 to 87.1)[d]	78.9 (75.7 to 81.8)[d]
Significant bowel disease (CRC or HRA or IBD)									
Mowat 2015[52]	0[b]	90	12	347	301	750	Reported	88.2 (80.4 to 93.8)[d]	46.5 (42.6 to 50.4)[d]
Mowat 2015[52]	≥ 10	70	32	106	542	750		68.6 (58.7 to 77.5)[d]	83.6 (80.6 to 86.4)[d]
Significant bowel disease (CRC or HRA or low-risk adenoma or IBD)									
McDonald 2012[13]	≥ 10[a]	49	37	2	192	280	Calculated	57.0 (45.8 to 67.6)	99.0 (96.3 to 99.9)

a Converted from 'ng Hb/ml buffer' using a multiplication factor of 0.2.[17,18]
b The limit of detection for the assay is 4 µg Hb/g faeces or 20 ng/ml buffer.
c Participants with CRC appear to have been classified as reference standard negative in this analysis.
d Calculated estimate.
e Sietze van Turenhout, personal communication; unpublished data provided in confidence.
f Participants with CRC were excluded from this analysis.
g Participants with CRC or HRA appear to have been classified as reference standard negative in this analysis.

TABLE 10 Acceptability of faecal immunochemical testing using OC-Sensor

Study	Point in the care pathway at which faecal immunochemical testing was requested	*n*	*n* returned	Uptake (%)
Mowat 2015[52]	Faecal immunochemical testing was requested by GPs at the point of referral to secondary care, and sampling devices and patient instruction sheets were distributed by practice nurses	2173	1043	48
Rodríguez-Alonso 2015[53]	Patients were given the specimen collection device at their initial consultation with a gastroenterologist	1054	1035	98
McDonald 2012[13]	Patients were sent an invitation to participate along with their referral letter. This was followed up by a telephone call from a research nurse. Sample collection devices and written and pictorial instructions were provided by post	739	306	41
Cubiella 2014 (COLONPREDICT)[55]	Patients were invited to participate after they had been referred for colonoscopy	825	799	97

n, number invited to participate in the study and supplied with a faecal sampling kit; *n* returned, number returning a faecal sample for faecal immunochemical testing.

Prediction modelling results from OC-Sensor faecal immunochemical testing studies

Rodríguez-Alonso *et al.*[53] also conducted multivariable analysis, using forward conditional logistic regression modelling, with the aim of identifying independent predictors of CRC and advanced neoplasia. The CRC analysis identified male gender (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; $p = 0.012$) and faecal Hb ≥ 10 µg Hb/g faeces (OR 86.60, 95% CI 11.70 to 641.16; $p < 0.001$) as independent predictors.[53] The advanced neoplasia analysis identified male gender (OR 2.36, 95% CI 1.50 to 3.40; $p < 0.001$), age (OR 1.36, 95% CI 1.13 to 1.63; $p < 0.001$) and faecal Hb ≥ 10 µg Hb/g faeces (OR 7.54, 95% CI 5.03 to 11.28; $p < 0.001$) as independent predictors; age was treated a categorical variable in this model (≤ 40 years, 41–60 years, 51–60 years, 61–70 years, ≥ 70 years).[53] None of the NICE or SIGN 2-week referral criteria was identified as an independent predictor in either model, provided that faecal Hb measured by faecal immunochemical testing was included in the model.[53] The results of modelling were used to derive a risk score for advanced neoplasia; the scoring system assigned integer values to each independent predictor based on their coefficients from the logistic regression model.[53] The score ranged from 0 to 11 points, with points assigned as follows: age < 40 years = 0 points, age 41–50 years = 1 point, age 51–60 years = 2 points, age 61–70 years = 3 points, age > 70 years = 4 points; female gender = 0 points, male gender = 2 points; faecal Hb of < 10 µg Hb/g faeces = 0 points and faecal Hb ≥ 10 µg Hb/g faeces = 5 points.[53] The model was validated using a split sampling technique [data from 680 study participants (67.8%) were used to develop the model and data from 323 participants (32.2%) were used for validation].[53] In the validation sample, a risk score of ≥ 5 had a sensitivity for advanced neoplasia of 88.1% (95% CI 74.3% to 96.0%) and a specificity of 63.3% (95% CI 57.4% to 69.0%).[53]

As part of the COLONPREDICT study,[55] Cubiella *et al*. have also developed a prediction model for CRC in symptomatic patients, based on FIT age and sex; this work has yet to be published in full, but was presented at the 2015 meeting of the World Endoscopy Association Colorectal Cancer Screening Committee.[73] A draft of the full paper reporting the development and validation of a risk score, the Faecal haemoglobin, Age and Sex Test (FAST) score, was provided ahead of publication (Callum Fraser, personal communication). The logistic regression model used to develop the FAST score included sex, age as a continuous variable and faecal Hb as a categorical variable (0, 0–20, 20–200, and ≥ 200 µg Hb/g faeces).[73] The validation cohort for this model used data from four studies[13,52,53,56] that are included in this systematic review, and an additional cohort recruited to the COLONPREDICT study[55] between March 2014 and March 2015; in this latter cohort, faecal immunochemical testing was measured using a variety of methods [OC-Sensor 202, OC-Auto 3 Latex (Eiken Chemical Co.) and FOB Gold]. The thresholds used to assess the performance of the FAST score in the

validation cohort corresponded to the beta coefficients of the FAST score with 90% and 99% sensitivity in the development cohort (4.5 and 2.12, respectively). In the validation cohort, 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 CRC. In order to avoid missing any CRCs, a lower FAST score threshold of ≥ 2.12 was required; the sensitivity and specificity estimates at this threshold were 100% (95% CI 97.7% to 100%) and 19.8% (95% CI 18.6% to 21.1%), respectively. Post hoc analysis indicated that there were no significant differences in FAST score performance, for the detection of CRC, when comparing patients referred for colonoscopy from primary care with those referred from secondary care; CRC prevalence in the validation cohort was similar in the two settings (5.6% in primary care and 4.9% in secondary care). The performance of the FAST score was also assessed for the detection of the expanded target conditions of advanced neoplasia (CRC or HRA) and significant colonic lesions; the definitions of these target conditions varied between the studies included in the validation cohort. Studies that were conducted in Scotland defined HRA as a lesion of ≥ 10 mm diameter or more than three lesions, and significant colonic lesions as CRC, HRA or IBD.[13,52,56] The published Spanish study[53] and the additional, unpublished cohort from the COLONPREDICT study[55] defined HRA as a lesion of ≥ 10 mm diameter or with villous histology or high-grade dysplasia; in these cohorts, the definition of significant colonic lesions included CRC, HRA, polyposis (> 10 polyps of any histology including serrated lesions), colitis, polyps of ≥ 10 mm, complicated diverticular disease, colonic ulcer or bleeding angiodysplasia). Sensitivity estimates for the lower FAST score threshold (2.12) remained high (≥ 95%) for all of the target conditions. For the target condition 'advanced neoplasia', the sensitivity estimates for the FAST score using the 4.5 and 2.12 thresholds were 60.7% (95% CI 56.6% to 64.7%) and 96.7% (95% CI 94.9% to 98.0%), respectively, and the corresponding specificity estimates were 85.4% (95% CI 84.1% to 86.5%) and 21.5% (95% CI 20.1% to 22.9%). For the target condition 'significant colonic lesion', the sensitivity estimates for the FAST score using the 4.5 and 2.12 thresholds were 57.8% (95% CI 54.3% to 61.3%) and 94.5% (95% CI 92.6% to 96.0%), respectively, and the corresponding specificity estimates were 87.4% (95% CI 86.2% to 88.5%) and 22.0% (95% CI 20.6% to 23.5%).

Diagnostic performance of the HM-JACKarc faecal immunochemical test assay

Details of HM-JACKarc studies

Three diagnostic cohort studies,[56,57,75] reported in seven publications,[56,57,65,66,71,72,75] provided data on the diagnostic performance of the HM-JACKarc FIT assay. Two studies[56,75] reported accuracy data, for which CRC was the specified target condition. The prevalence of CRC, diagnosed at colonoscopy, was 2.2% in the Godber *et al.* study[56] and 4.9% in the Thomas *et al.* study.[75] One of the CRC studies[56] and one additional study[57] also reported data for the composite target condition of advanced neoplasia (CRC or HRA). Each of the studies used a different definition of HRA; Auge *et al.*[57] defined HRA based on size, morphology or number of lesions (any lesion of ≥ 10 mm in diameter or with villous architecture or high-grade dysplasia, or three or more non-advanced adenomas) and Godber *et al.*[56] defined higher-risk adenoma, based on size or number of lesions, using a combination of the BSG categories 'high risk' (five or more adenomas or three or more adenomas, at least one of which is of ≥ 10 mm in diameter) and 'intermediate risk' (three or four small adenomas or at least one adenoma of ≥ 10 mm in diameter).[90] Two studies[56,75] reported additional accuracy data for various non-malignant and composite target conditions.

No study reported data that were specific to the population that was defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1]). No studies were conducted in a primary care setting; all three of the studies[56,57,75] were conducted in outpatient clinics. One study[56] stated that faecal immunochemical testing was requested after referral for colonoscopy, and in the remaining two studies[57,75] the timing of faecal immunochemical testing in relation to colonoscopy referral was unclear. One study,[75] reported as a conference abstract, stated that only symptomatic patients were included, but did not report details of presenting symptoms. The remaining two studies[56,57] included patients who had been referred for colonoscopy, and one study[56] recorded presenting symptoms (reason for referral); both of the studies[56,57] that reported presenting symptoms included some participants who had symptoms that may be

considered to be associated with a higher probability of CRC and that are components of the criteria for 2-week referral as defined in NG12[1] (e.g. rectal bleeding). Presenting symptoms included rectal bleeding/haematochezia, abdominal pain, change in bowel habit, constipation or diarrhoea, anaemia and weight loss. The median age of study participants was 67 years,[75] 63 years[57] and 59 years,[56] and the overall age range was 16–93 years. There were no data linking presenting symptoms to age. One study[57] reported data on the effects of the sex of participants on the accuracy of HM-JACKarc for the detection of advanced neoplasia. Full details of participant characteristics are provided in *Appendix 2*, *Table 65*.

All of the three studies[56,57,75] reported data on the accuracy of HM-JACKarc FIT using a single faecal sample. One study[57] also compared the accuracy of single versus double sampling faecal immunochemical testing for the detection of advanced neoplasia.

Two studies reported information about uptake rates in participants invited to provide a sample for faecal immunochemical testing.[56,75]

Accuracy of HM-JACKarc for the detection of colorectal cancer

Two studies[56,75] reported data on the accuracy of HM-JACKarc FIT using a single faecal sample and thresholds of 10 µg Hb/g faeces[56] and 7 µg Hb/g faeces.[75] Full test performance results are provided in *Table 11*. There was little variation in test performance between the 7- and 10 µg Hb/g faeces thresholds; the sensitivity estimates were 91.3% and 100%, respectively, and the corresponding specificity estimates were 76.6% and 79.2%.[56,75] As with the OC-Sensor FIT assay, the optimal test performance (maximising both sensitivity and specificity) appeared to occur with thresholds of 7 or 10 µg Hb/g faeces; none of the HM-JACKarc studies reported test performance characteristics for any detectable Hb. Using test performance data from the Godber *et al.* study[56] – and a CRC prevalence estimate of 2.2% taken from the same study – to consider the outcome of testing for a hypothetical cohort of 1000 patients indicates that no CRCs would be missed using the 10 µg Hb/g faeces threshold, but 229 unnecessary colonoscopies would be carried out (assuming that all of the patients with a positive FIT result receive colonoscopy and that all colonoscopies conducted in patients without CRC are considered unnecessary). CRC would be correctly ruled out in 750 people (*Figure 8*). Please see subsequent sections for information on other significant bowel pathologies that may be detected by faecal immunochemical testing and hence may form part of the FP or 'unnecessary colonoscopy' population.

Accuracy of HM-JACKarc for the detection of advanced neoplasia (colorectal cancer or high-risk adenoma)

Two studies[56,57] reported data on the accuracy of HM-JACKarc FIT using a single faecal sample, for which the target condition was expanded to include CRC or HRA. Two studies[56,57] assessed the diagnostic performance of the 10 µg Hb/g faeces threshold for different definitions of this expanded target condition (see *Details of HM-JACKarc studies*, above); these two studies[56,57] reported very different estimates of sensitivity (70% and 34.5%, respectively). In addition to the difference in the definition of HRA, the Auge *et al.* study[57] differed from Godber *et al.* study[56] in that it included some patients who were undergoing

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

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
[a]Godber 2016[56]	≥ 10	11	0	116	380	507	Reported	100 (71.5 to 100)[b]	76.6 (72.6 to 80.3)[b]
[a]Thomas 2016[75]	≥ 7	21	2	89	338	450	Calculated	91.3 (72.0 to 98.9)	79.2 (75.3 to 83)

a Personal communication (e-mail from Ian Godber; Biochemistry Department, Monklands Hospital, NHS Lanarkshire, to Marie Westwood, KSR Ltd, 8 June 2016).
b Calculated estimate.

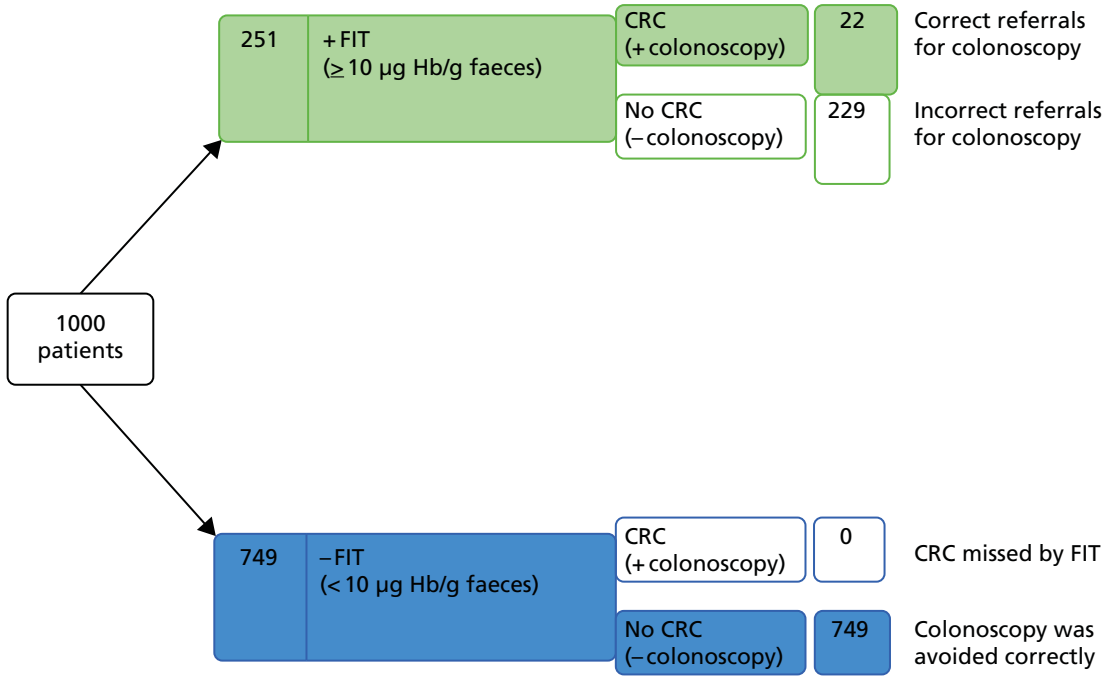

FIGURE 8 Testing outcomes for a hypothetical cohort of 1000 patients using HM-JACKarc: the 10 µg Hb/g faeces threshold, for the target condition of CRC.

colonoscopy for polyp surveillance and excluded people with GI bleeding or active rectal bleeding; the prevalence of CRC in the Auge *et al.* study[57] was the lowest of any study included in this review (0.96%).[57] Auge *et al.*[57] reported test performance characteristics using a range of thresholds; sensitivity decreased and specificity increased with increasing threshold, and the 'any detectable Hb' threshold was associated with high sensitivity (96.6%) and very low specificity (10.6%). Full test performance results for all of the thresholds that were evaluated in individual studies are provided in *Table 12*. The variation in test performance characteristics according to the threshold used is illustrated in a ROC space plot (*Figure 9*).

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

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Any detectable Hb									
Auge 2016[57]	0[a]	28	1	160	19	208	Calculated	96.6 (82.8 to 93.4)	10.6 (6.9 to 15.9)
10 µg Hb/g faeces									
Auge 2016[57]	≥ 10	10	19	23	156	208	Calculated	34.5 (19.9 to 52.7)	87.2 (81.6 to 91.3)
[b]Godber 2016[56]	≥ 10	21	9	106	371	507	Reported	70.0 (50.6 to 85.3)[c]	77.8 (73.8 to 81.4)[c]
Other thresholds									
Auge 2016[57]	≥ 20	9	20	13	166	208	Calculated	31 (17.3 to 49.2)	92.8 (88 to 95.7)
	≥ 30	9	20	12	167	208		31 (17.3 to 49.2)	93.3 (88.7 to 96.1)
	≥ 40	8	21	11	168	208		27.6 (14.7 to 45.7)	93.9 (89.4 to 96.6)

a The limit of detection for the assay is 0.6 µg Hb/g faeces or 0.6 ng/ml buffer.
b Ian Godber, personal communication.
c Calculated estimate.

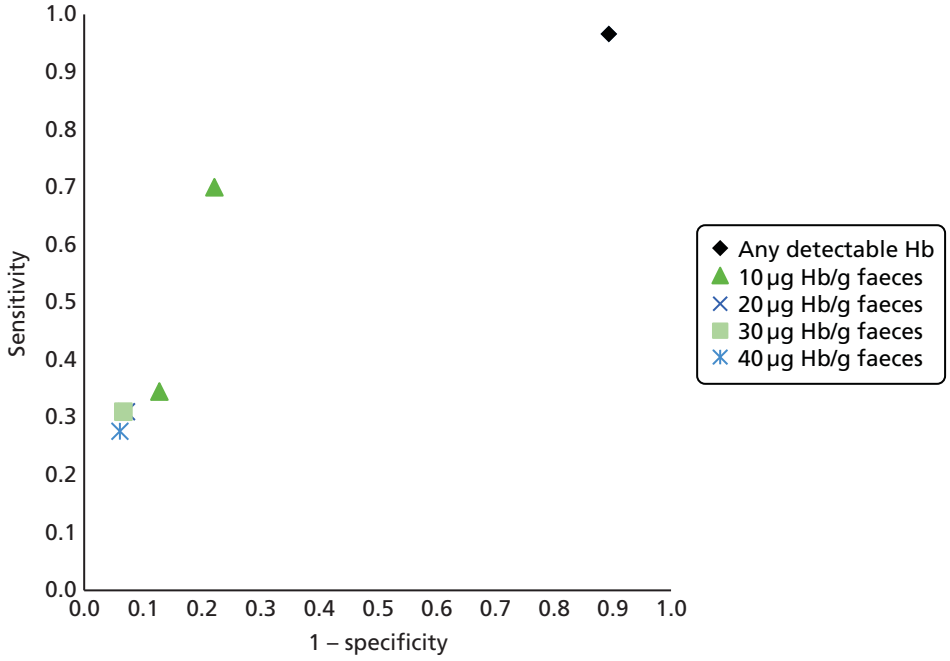

FIGURE 9 Receiver operating characteristic space plot for the HM-JACKarc assay using different thresholds for the target condition of advanced neoplasia (CRC or HRA).

Based on the data from Godber *et al.*,[56] expanding the target condition from CRC only to include CRC or HRA resulted in an increase in prevalence from 2.2% to 5.9%. Using test performance data from this study – and an estimate for the prevalence of advanced neoplasia of 5.9% – to consider the outcome of testing for a hypothetical cohort of 1000 patients indicates that applying faecal immunochemical testing at the 10 µg Hb/g faeces threshold would result in 21 advanced neoplasias being missed. As data indicate that no CRCs would be missed at this threshold (see previous section), it may be assumed that the missed cases would all be higher-risk adenomas. Using the 10 µg Hb/g faeces threshold, 205 unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and that all of the colonoscopies that were conducted in patients without at least HRA are considered unnecessary); CRC and higher-risk adenoma would be correctly ruled out in 727 people (*Figure 10*).

Data from Auge *et al.* study[57] indicated that, in this population (CRC prevalence < 1%), high sensitivity (good rule-out performance) could be achieved only by using the 'any detectable Hb' threshold; the sensitivity at this threshold was 96.6%. This study[57] also compared the performance of double sampling with single sampling, and found that 100% sensitivity could be achieved by using the higher value from two consecutive samples and the 'any detectable Hb' threshold. The use of two consecutive samples increased sensitivity compared with single sampling, at all thresholds, but sensitivity remained low (< 50%) throughout.[57] Full results for single and double sampling at all of the thresholds that were evaluated are provided in *Table 13*.

Auge *et al.*[57] also reported lower sensitivity estimates, at all thresholds, when HM-JACKarc FIT was used, in women than in men.[57] Full results for test performance in men and women are provided in *Table 14*.

Accuracy of HM-JACKarc for the detection of other/composite target conditions

Two studies[56,75] reported accuracy data for target conditions other than CRC or advanced neoplasia. Both of the studies evaluated the performance of HM-JACKarc for the target condition 'significant bowel disease'; Thomas *et al.*[75] defined significant bowel disease as CRC, HRA or IBD, and Godber *et al.*[56] defined significant bowel disease as CRC, higher-risk adenoma, IBD or colitis.

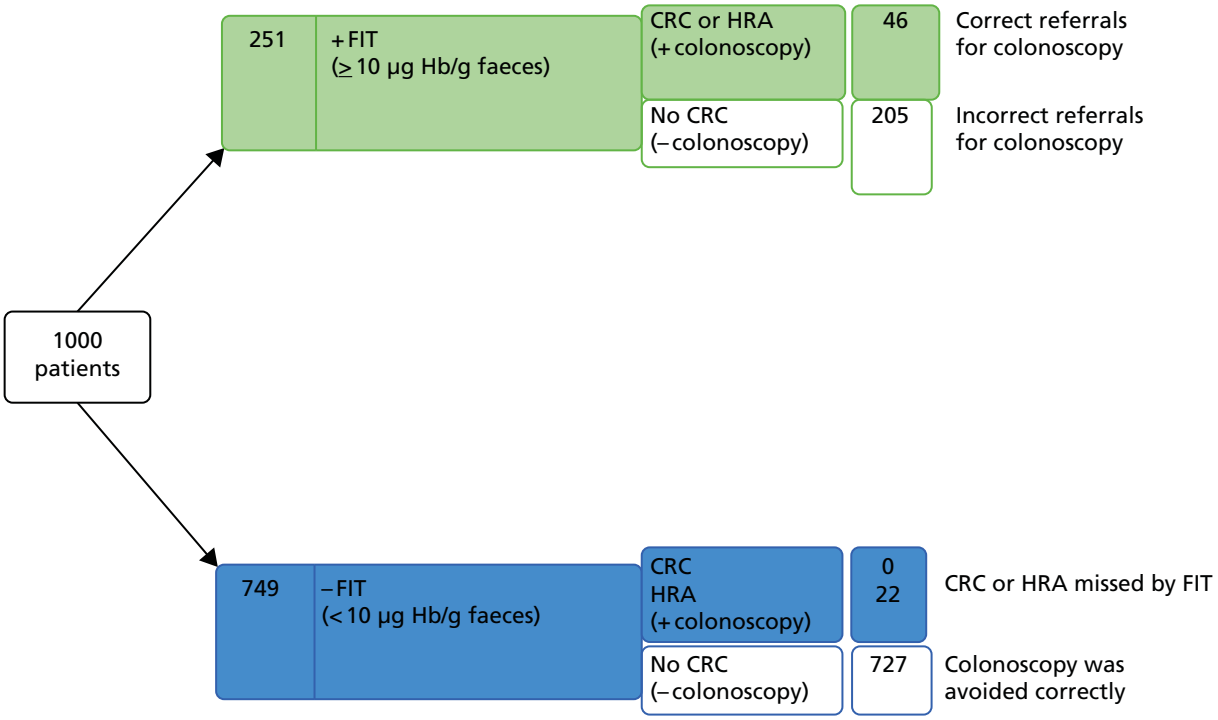

FIGURE 10 Testing outcomes for a hypothetical cohort of 1000 patients using HM-JACKarc: the 10 µg Hb/g faeces threshold for the target condition of advanced neoplasia (CRC or HRA).

TABLE 13 Effects of multiple sampling on the accuracy of HM-JACKarc for the detection of advanced neoplasia (CRC or HRA)

Study	Sampling strategy	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Auge 2016[57]	First of two consecutive samples	0[a]	28	1	160	19	208	Calculated	96.6 (82.8 to 93.4)	10.6 (6.9 to 15.9)
	Higher of two consecutive samples	0[a]	29	0	173	6	208		100 (88.3 to 100)	3.3 (1.5 to 7.1)
	First of two consecutive samples	≥ 10	10	19	23	156	208		34.5 (19.9 to 52.7)	87.2 (81.6 to 91.3)
	Higher of two consecutive samples	≥ 10	12	17	37	142	208		41.4 (25.5 to 59.3)	79.4 (73 to 84.7)
	First of two consecutive samples	≥ 20	9	20	13	166	208		31 (17.3 to 49.2)	92.8 (88 to 95.7)
	Higher of two consecutive samples	≥ 20	10	19	26	153	208		34.5 (19.9 to 52.7)	85.6 (83.5 to 92.9)
	First of two consecutive samples	≥ 30	9	20	12	167	208		31 (17.3 to 49.2)	93.3 (88.7 to 96.1)

continued

TABLE 13 Effects of multiple sampling on the accuracy of HM-JACKarc for the detection of advanced neoplasia (CRC or HRA) (*continued*)

Study	Sampling strategy	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
	Higher of two consecutive samples	≥ 30	10	19	25	154	208		34.5 (19.9 to 52.7)	86.1 (83.6 to 92.9)
	First of two consecutive samples	≥ 40	8	21	11	168	208		27.6 (14.7 to 45.7)	93.9 (89.4 to 96.6)
	Higher of two consecutive samples	≥ 40	10	19	21	158	208		34.5 (19.9 to 52.7)	88.3 (82.8 to 92.2)

a The limit of detection for the assay is 0.6 µg Hb/g faeces or 0.6 ng/ml buffer.

TABLE 14 Effects of participant sex on the accuracy of HM-JACKarc for the detection of advanced neoplasia (CRC or HRA) using a single faecal sample

Study	Subgroup	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Auge 2016[57]	Men	0[a]	17	0	69	6	92	Calculated	100 (81.6 to 100)	8 (3.7 to 16.4)
	Women	0[a]	11	1	91	13	116		91.7 (64.6 to 98.5)	12.4 (7.4 to 20)
	Men	≥ 10	8	9	10	65	92		47.1 (26.2 to 69)	86.7 (77.2 to 92.6)
	Women	≥ 10	2	10	13	91	116		16.7 (4.7 to 44.8)	87.6 (79.8 to 92.6)
	Men	≥ 20	7	10	6	69	92		41.2 (21.6 to 64)	92 (83.6 to 96.3)
	Women	≥ 20	2	10	7	97	116		16.7 (4.7 to 44.8)	93.3 (86.8 to 96.7)
	Men	≥ 30	7	10	6	69	92		41.2 (21.6 to 64)	92 (83.6 to 96.3)
	Women	≥ 30	2	10	6	98	116		16.7 (4.7 to 44.8)	94.3 (88 to 97.3)
	Men	≥ 40	7	10	6	69	92		41.2 (21.6 to 64)	92 (83.6 to 96.3)
	Women	≥ 40	1	11	5	99	116		8.3 (1.5 to 35.4)	95.2 (89.3 to 97.9)

a The limit of detection for the assay is 0.6 µg Hb/g faeces or 0.6 ng/ml buffer.

Thomas *et al.*[75] reported sensitivity and specificity estimates of 72.1% and 80.6%, using a threshold of 7 µg Hb/g faeces, but did not provide sufficient information to extract 2 × 2 data,[75] and Godber *et al.*[56] reported similar sensitivity and specificity estimates of 68.9% and 80.2% for the 10 µg Hb/g faeces threshold.[56] Because the Godber *et al.* study[56] assessed both this composite target condition and CRC alone in the same patient cohort, we can see that the small increase in the specificity estimate, relative to that reported for CRC, means that 26 of the 116 participants (22.4%) who were classified as having FP FIT results for CRC actually had other significant bowel pathologies (HRA, IBD or colitis) and may thus have benefited from secondary care investigation.

Godber *et al.*[56] also reported test performance data using a range of thresholds from 10 to 40 µg Hb/g faeces; there was little variation in the sensitivity and specificity of HM-JACKarc for 'significant bowel disease' with increasing threshold.[56] Full results for the accuracy of HM-JACKarc for detecting 'significant bowel disease', at all thresholds investigated, are provided in *Table 15*.

TABLE 15 Accuracy of HM-JACKarc for the detection of other/composite target conditions using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Significant bowel disease (CRC or HRA or IBD)									
Thomas 2016[75]	≥ 7 µg Hb/g faeces	NC	NC	NC	NC	450	NA	72.1 (58.7 to 85.5)	80.6 (76.7 to 84.4)
Significant bowel disease (CRC or higher-risk adenoma or IBD or colitis)									
Godber 2016[56]	≥ 10 µg Hb/g faeces	32	13	90	349	484	Calculated	68.9 (53.2 to 81.4)	80.2 (76.1 to 83.7)
	≥ 20 µg Hb/g faeces	29	16	63	376	484		64.4 (48.7 to 77.7)	85.7 (81.9 to 88.7)
	≥ 15 µg Hb/g faeces	31	14	77	362	484		66.7 (50.9 to 79.6)	83.1 (79.2 to 86.5)
	≥ 25 µg Hb/g faeces	29	16	55	384	484		64.4 (48.7 to 77.7)	87.5 (83.9 to 90.3)
	≥ 30 µg Hb/g faeces	29	16	50	389	484		64.4 (48.7 to 77.7)	88.6 (85.2 to 91.4)
	≥ 35 µg Hb/g faeces	29	16	47	392	484		64.4 (48.7 to 77.7)	89.2 (85.9 to 92)
	≥ 40 µg Hb/g faeces	29	16	44	395	484		64.4 (48.7 to 77.7)	90 (86.7 to 92.5)

NA, not applicable; NC, not calculable.

Acceptability of faecal immunochemical testing using HM-JACKarc

The proportion of people invited to participate in faecal immunochemical testing who return a faecal sample can be regarded as a possible indicator of the acceptability of faecal immunochemical testing. Two[56,75] of the four HM-JACKarc studies reported FIT uptake rates. The proportion of samples returned was higher (66%) in the study for which information and collection devices were provided at an outpatient appointment[75] than in the study that sent collection devices and information by post (56%).[56] Full results are provided in *Table 16*.

TABLE 16 Acceptability of faecal immunochemical testing using HM-JACKarc

Study	Point in the care pathway at which faecal immunochemical testing was requested	*n*	*n* returned	Uptake (%)
Thomas 2016[75]	Faecal immunochemical testing was requested after the first secondary care 2-week wait clinic. Participants were given a pack that included a sample collection device and pictorial instructions	773	514	66
Godber 2016[56]	Patients were invited to participate after they had been referred for colonoscopy. A letter of invitation to participate and a sample collection device were sent with the materials sent for bowel cleansing prior to colonoscopy	909	507	56

n, number invited to participate in the study and supplied with a faecal sampling kit; *n* returned, number returning a faecal sample for faecal immunochemical testing.

Diagnostic performance of the FOB Gold faecal immunochemical test assay

Details of FOB Gold studies

Two diagnostic cohort studies provided data on the diagnostic performance of the FOB Gold FIT assay; the Krivec *et al.* study[54] was published as an conference abstract and provided only limited data,[54] and the other, Hospital Clinic de Barcelona 2015, was provided in confidence by the manufacturer (Philippa Pinn, personal communication). Krivec *et al.*[54] reported accuracy data for significant bowel disease (defined as cancer polyps or bleeding) and Hospital Clinic de Barcelona 2015 (confidential information has been removed). The prevalence of CRC was not reported in the Krivec *et al.* study[54] (confidential information has been removed).

No study clearly reported data that were specific to the population that was defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms, who are at low risk for CRC according to the criteria defined in NG12[1]). Both study populations were reported as symptomatic patients who had been referred for colonoscopy. Krivec *et al.*[54] did not report any information about the age of participants[54] (confidential information has been removed). No details of presenting symptoms were reported in either study. Full details of participant characteristics are provided in *Appendix 2*, *Table 65*.

Neither study reported information about uptake rates in participants who were invited to provide a sample for faecal immunochemical testing, or any other outcome measure.

Accuracy of FOB Gold for the detection of colorectal cancer

(Confidential information has been removed.) Full test performance results for all thresholds evaluated are provided in *Table 17*. (Confidential information has been removed), to consider the outcome of testing for a hypothetical cohort of 1000 patients indicates that (confidential information has been removed). CRCs would be missed and (confidential information has been removed) unnecessary colonoscopies would be carried out (assuming that all patients with a positive FIT result receive colonoscopy and that all colonoscopies conducted in patients without CRC are considered unnecessary); CRC would be correctly ruled out by faecal immunochemical testing, avoiding colonoscopy, in (confidential information has been removed) people (*Figure 11*).

Accuracy of FOB Gold for the detection of advanced neoplasia (colorectal cancer or high-risk adenoma)

(Confidential information has been removed.) Full test performance results for all of the strategies evaluated are provided in *Table 18*.

Accuracy of FOB Gold for the detection of other/composite target conditions

Both Krivec *et al.*[54] and Hospital Clinic de Barcelona 2015 reported accuracy data for the composite target condition 'significant bowel disease'. Krivec *et al.*[54] defined significant bowel disease as cancer, polyps or bleeding, and reported a sensitivity of 45.2% and a specificity of 92.3%, using a threshold of 9 µg Hb/g faeces.[54] (Confidential information has been removed.) Full test performance results for both studies and for all thresholds evaluated are provided in *Table 19*.

(Confidential information has been removed.) Full test performance results for all thresholds evaluated are provided in *Table 19*.

TABLE 17 Accuracy of FOB Gold for the detection of CRC using a single faecal sample

Study	Threshold (μg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

a Philippa Pinn, personal communication.
(Confidential information has been removed.)

FIGURE 11 (Confidential information has been removed.)

TABLE 18 Accuracy of FOB Gold for the detection of advanced neoplasia (CRC or HRA) using single and double sampling regimens

Study	Sampling strategy	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

a Philippa Pinn, personal communication.
(Confidential information has been removed.)

TABLE 19 Accuracy of FOB Gold for the detection of other/composite target conditions using a single faecal sample

Study	Threshold (µg Hb/g faeces)	TP	FN	FP	TN	Total *n*	2 × 2 data	Sensitivity % (95% CI)	Specificity % (95% CI)
All neoplasia (cancer or HRA or low-risk adenoma)									
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Significant bowel disease (CRC, HRA, low-risk adenoma, hyperplastic or inflammatory polyps, IBD, haemorrhoids, diverticulosis, angiodysplasia, other)									
Hospital Clinic de Barcelona 2015[a]	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Significant bowel disease (CRC polyps or bleeding)									
Krivec 2011[54]	≥ 9[b]	NC	NC	NC	NC	83	NA	45.2 (NC to NC)	92.3 (NC to NC)

NA, not applicable; NC, not calculable.
a Philippa Pinn, personal communication.
b Converted from ‘ng Hb/ml buffer’ using a multiplication factor of 0.17.[17,18]

Diagnostic performance of the RIDASCREEN faecal immunochemical test assay

No studies were identified that assessed the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients.

Comparative diagnostic accuracy of different faecal immunochemical test assays and guaiac faecal occult blood testing

No studies were identified that directly compared the performance of different FIT assays, or that compared one or more FIT assays with a gFOBT method.

Selection of test strategies for inclusion in cost-effectiveness modelling

The selection of FIT accuracy data for use in cost-effectiveness modelling was based on the optimal threshold (maximum sensitivity and specificity) for each assay method and the threshold required to proved optimal rule-out performance (highest sensitivity and lowest number of cases missed). Because no studies were identified which directly compared the performance of one or more FIT assays with a gFOBT method, accuracy data for guaiac faecal occult blood testing used in the base case for cost-effectiveness modelling were those used in the NG12[6] model. The primary study from which these data were taken, Gilbert *et al.*,[91] was a retrospective study using a Swedish cancer registry, in which a diagnosis of CRC was classified as any diagnosed CRC within 2 years of guaiac faecal occult blood testing; it was unclear whether or not all of the patients who were included in the study had been symptomatic at the time of guaiac faecal occult blood testing, and the prevalence of CRC, in the subgroup of study participants used to provide data for the model was very low (0.36%). We therefore conducted scenario analyses using published estimates of gFOBT accuracy obtained from studies that were identified during the process of inclusion screening for our systematic review: Niv and Sperber[92] and Bjerregaard *et al.*;[93] although guaiac faecal occult blood testing was not included in our systematic review, as an intervention, our searches included general terms for faecal occult blood testing and guaiac faecal occult blood testing. Both of these studies[92,93] were conducted in symptomatic patients and the prevalence of CRC was 2.5% and 3.1%, respectively, making these studies closer to the population defined for this assessment.

Chapter 4 Assessment of cost-effectiveness

In this chapter we explore the cost-effectiveness of using quantitative faecal immunochemical tests for Hb (FIT) as a triage test for people presenting, in primary care settings, with lower abdominal symptoms who are at low risk for CRC according to the criteria defined in NG12.[1]

Review of economic analyses of faecal immunochemical tests

Methods

Search strategy

Literature searches were performed to identify published economic evaluations and cost-effectiveness data. Additional searches were conducted to identify adverse event/mortality data and utility studies for diagnostic techniques and procedures for colorectal neoplasms that were not included within the scope of the clinical effectiveness searches. All of the searches aimed to identify studies that could be used to support the development of a health economic model to estimate the model input parameters and answer the research questions of the assessment, but not to perform a systematic review. Searches were therefore pragmatic in design and date limits were applied where appropriate.

Methodological study design filters were included in the search strategy where relevant. No restrictions on language or publication status were applied. The main EMBASE strategy for each search was independently peer reviewed by a second Information Specialist, using the CADTH Peer Review checklist.[40] Identified references were downloaded in EndNote X6 software for further assessment and handling. References in retrieved articles were checked for additional studies.

Full search strategies are presented in *Appendix 1*.

Full cost-effectiveness studies were summarised and appraised using the Drummond checklist.[94]

Economic evaluations and cost studies

Economic evaluations and cost studies associated with colonoscopy, CTC, magnetic resonance imaging and computed tomography (CT) scans were searched for on the following databases and resources, from 2005 to the most recent date available:

- MEDLINE (via Ovid): 2005 to March Week 4 2016
- MEDLINE In-Process & Other Non-Indexed Citations, and Daily Update (via Ovid): 2005 to 1 April 2016
- EMBASE (via Ovid): 2005 to 1 April 2016
- NHS EED (via the internet): 2005 to Issue 2 of 4, April 2015
- EconLit (via EBSCO*host*): 2005 to 1 February 2016
- Cost-effectiveness Analysis Registry (via the internet): 2005 to April 2016: www.cearegistry.org/
- Research Papers in Economics (via the internet): 2005 to April 2016: http://repec.org/.

Adverse events and mortality data

Adverse events and mortality data that are associated with colonoscopy and CTC were searched for on the following databases and resources, from database inception date to the most recent date available:

- MEDLINE (via Ovid): 1946 to March Week 4 2016
- MEDLINE In-Process & Other Non-Indexed Citations, and Daily Update (via Ovid): to 4 April 2016
- EMBASE (via Ovid): 1974 to 4 April 2016
- CENTRAL (via the internet): to Issue 3 of 12, March 2016.

Utility data

Studies containing utility data that are associated with colonoscopy and CTC were searched for on the following databases and resources, from database inception date to the most recent date available:

- MEDLINE (via Ovid): 1946 to March Week 4 2016
- MEDLINE In-Process & Other Non-Indexed Citations Daily Update (via Ovid): to 4 April 2016
- EMBASE (via Ovid): 1974 to 4 April 2016
- CENTRAL (via the internet): to Issue 3 of 12, March 2016
- NHS EED (via the internet): 2005 to Issue 2 of 4, April 2015
- School of Health and Related Research (ScHARR) Health Utilities Database (ScHARRHUD) (via the internet): to 4 April 2016. www.scharrhud.org/.

Inclusion criteria and screening

Inclusion criteria as reported in *Table 20* were applied. Relevant studies were identified in two stages. Two researchers (ML and ICR) screened, independently, for possible inclusion, the titles and abstracts that were returned by the search strategy. Disagreements were resolved by discussion. Full texts of the selected studies were obtained. Two researchers (ML and ICR) examined these independently for inclusion or exclusion, and disagreements were, again, resolved by discussion.

Results

The total number of potentially relevant economic papers that were initially retrieved by searches was 923. In addition, 19 clinical guidelines relating to CRC were identified. Most of the economic studies that were identified were excluded because they related to screening for CRC in asymptomatic populations. None of the included studies directly assessed the decision problem of this diagnostic assessment.

The only included study was the one conducted to inform NG12.[1,6] This study[1,6] is reviewed in detail below.

Summary of the National Institute for Health and Care Excellence guideline 12 cost-effectiveness study

The aim of the NG12 study[1,6] was to estimate the cost-effectiveness of five different investigations for suspected CRC (FOBT, barium enema, flexible sigmoidoscopy, CTC or colonoscopy) ordered by primary care practitioners for patients aged $\geq$ 40 years with a change in bowel habit as main symptom.[6] The characteristics of this study are summarised in *Table 21*. The base-case results indicated that both guaiac faecal occult blood testing and barium enema were cost-effective compared with colonoscopy at a threshold of £20,000 per quality-adjusted life-year (QALY) gained. However, an analysis that included all of the comparators showed that barium enema would have been dominated by faecal immunochemical testing [the incremental cost-effectiveness ratio (ICER) for faecal immunochemical testing vs. barium enema being lower than barium enema vs. guaiac faecal occult blood testing] and that faecal immunochemical testing would be cost-effective at a threshold of £20,000 per QALY gained.

TABLE 20 Inclusion criteria for cost-effectiveness studies

Type of studies	Studies reporting cost-effectiveness/utility/benefit/minimisation analyses or economic evaluations in general. No study design restrictions were applied. All of the studies were included, apart from reviews, letters and comment articles
Type of participants	Symptomatic people presenting in primary care settings in whom investigation for possible CRC is being considered
Type of intervention	FIT
Type of outcomes	Costs or incremental costs and QALYs or other effectiveness units, such as LYs, reported together with costs

LY, life-year; QALY, quality-adjusted life-year.

TABLE 21 Summary of included full papers

Study, year, country	Summary of model	Investigations[a]	Patient population	Costs (£) per 1000 patients (all investigations)	QALYs per 1000 patients (all investigations)	ICER (per QALY gained)	Sensitivity analyses
NG12 2015[1,6]	• Decision tree analysis for diagnosis and Markov model for progression of colorectal cancer • UK NICE perspective • Time horizon: 40 years • Discount rate 3.5% for costs and effects • Data from systematic review when available. Otherwise from clinical expert opinion • Utilities: cancer stages from Ness *et al.*[95] (USA, standard gamble technique). Healthy patients from Kind *et al.*[96] (UK, EQ-5D) • Deterministic and PSA conducted	Base case: • FOBT • barium enema • colonoscopy Scenarios: • flexible sigmoidoscopy • CTC • FIT • safety netting	People aged ≥ 40 years with a change in bowel habit as a main symptom who have presented to their GP for the first time	• FOBT = 343,244 • Barium enema = 810.94 • FIT = 377,839 • Flexible sigmoidoscopy = 690,542 • CTC = 710,146 • Colonoscopy = 810,397 • Safety netting = 855,397	• FOBT = 809.99 • Barium enema = 365,818 • FIT = 812.34 • Flexible sigmoidoscopy = 811.76 • CTC = 814.38 • Colonoscopy = 814.24 • Safety netting = 814.24	ICERs (all comparators included); FOBT = NA • Barium enema = £23,731 • FIT = £14,705 Flexible sigmoidoscopy = dominated • CTC = £163,465 • Colonoscopy = £227,696 Safety netting = £251,851	• Sensitivity analysis for the base case only suggested that results were sensitive to sensitivity, specificity, cost and prevalence • PSA indicated that at a threshold of £20,000 per QALY, the probability of faecal occult blood testing being the most cost-effective investigation was 76%

EQ-5D, EuroQol-5 Dimensions; FOBT, faecal occult blood test; PSA, probabilistic sensitivity analysis.
a Using the terminology in NG12,[1] the economic evaluation is assessing the cost-effectiveness of five different *investigations* and it is not presented in terms of intervention vs. comparators.

Study quality

The results of the quality assessment of the NG12 study[1,6] are presented in *Table 22*.

TABLE 22 Quality assessment of studies, using the Drummond checklist

Criteria	NG12,[1,6] 2015
Study design	
1. Was the research question stated?	Yes
2. Was the economic importance of the research question stated?	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes
5. Were the alternatives being compared clearly described?	No. It is not mentioned which individual tests are considered to model faecal occult blood testing and faecal immunochemical testing. The other investigations considered in the analysis (i.e. barium enema, flexible sigmoidoscopy, CTC and colonoscopy) are not described in detail in the economic evaluation section, but discussed throughout the clinical guideline
6. Was the form of economic evaluation stated?	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes
Data collection	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No. For some investigations considered (e.g. accuracy of colonoscopy or CTC), only the reference to a paper is given
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes
12. Were the methods used to value health states and other benefits stated?	Yes
13. Were the details of the subjects, from whom valuations were obtained, given?	NA; utilities from literature
14. Were productivity changes (if included) reported separately?	NA
15. Was the relevance of productivity changes to the study question discussed?	NA
16. Were quantities of resources reported separately from their unit cost?	No
17. Were the methods for the estimation of quantities and unit costs described?	No
18. Were currency and price data recorded?	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No. The only reference to price inflation is the following sentence: 'Data on lifetime costs were taken from Tappenden *et al.* 2004 and inflated to 2014 prices'
20. Were details of any model used given?	Yes
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes

TABLE 22 Quality assessment of studies, using the Drummond checklist (*continued*)

Criteria	NG12,[1,6] 2015
Analysis and interpretation of results	
22. Was the time horizon of cost and benefits stated?	Yes
23. Was the discount rate stated?	Yes
24. Was the choice of rate justified?	Yes
25. Was an explanation given if cost or benefits were not discounted?	NA
26. Was/were the details of statistical test(s) and CIs given for stochastic data?	Not explicitly but CIs and/or standard errors reported (including reference)
27. Was the approach to sensitivity analysis described?	Yes
28. Was the choice of variables for sensitivity analysis justified?	Not explicitly but references reported
29. Were the ranges over which the parameters were varied stated?	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes
31. Was an incremental analysis reported?	Yes
32. Were major outcomes presented in a disaggregated form as well as aggregated form?	No, only aggregated
33. Was the answer to the study question given?	Yes
34. Did conclusions follow from the data reported?	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes
36. Were generalisability issues addressed?	No

NA, not applicable.

Study design

The economic evaluation presented in NG12[6] was a modelling study to assess the cost-effectiveness of different investigations for CRC. The research question and the approach to economic evaluation were stated clearly. Results were presented as costs per QALY gained. In the base-case analysis, the investigations considered were faecal occult blood testing, barium enema and colonoscopy. In additional scenarios, flexible sigmoidoscopy, CTC, faecal immunochemical testing and safety netting were incorporated to the analysis. Results were presented in the form of full incremental analysis (i.e. all investigations compared at the same time) and not in terms of pairwise comparisons of intervention against comparator. When faecal occult blood testing and faecal immunochemical testing were considered, it was not mentioned which individual assays are used to determine the input parameters of the model.

Data

When possible, the data that were used to inform the model input parameters were based on the systematic literature review conducted in the clinical guideline. Otherwise, there was reliance on expert opinion. A summary of the data sources for the different groups of input parameters is given below.

Prevalence of colorectal cancer

No evidence was found to inform the prevalence of CRC in the study population. Thus, the PPV of various symptoms associated with CRC was used to inform this. The systematic review identified 22 studies as relevant, but the evidence could not be pooled due to large heterogeneity. Therefore, the prevalence of CRC was estimated based on the opinion of the guideline development group (GDG).

Natural history of disease

The initial distributions of cancer stages at diagnosis and disease-specific mortality were estimated using data from the National Cancer Intelligence Network (NCIN).[97] Age-related mortality probabilities were calculated using data from published interim life tables for the UK ONS 2013.[98] The study from Tappenden *et al.*[99] reports data on progression between cancer stages for people with undiagnosed CRC. As the GDG considered that obtaining progression probabilities in patients with CRC would be unlikely, the probabilities in Tappenden *et al.*[99] were used in the model.

Diagnostic accuracy

Diagnostic accuracy was modelled using data on sensitivity and specificity from the systematic review. Six papers were identified as relevant for faecal occult blood testing and three for barium enema. However, the sensitivity and specificity reported in those papers could not be pooled because of the large heterogeneity between the studies. Therefore, based on the GDG advice, the paper by Gillberg *et al.*[91] was used for the diagnostic accuracy of faecal occult blood testing, and the paper by Jensen *et al.*[100] was chosen for barium enema. For the remaining interventions that were considered in the decision problem, no relevant evidence was identified. Data for these investigations were then collected by removing the 'primary care' filter from the search. The following papers were considered to inform the accuracy of the remaining investigations: Oono *et al.*[101] for faecal immunochemical testing, Thompson *et al.*[102] for flexible sigmoidoscopy, Pickhardt *et al.*[103] (only sensitivity) and Halligan *et al.*[104] for CTC, and Pickhardt *et al.*[103] for colonoscopy.

Adverse events

It was assumed that only colonoscopy and flexible sigmoidoscopy would require treatment for adverse events. Data on adverse events that were associated with colonoscopy were obtained from the UK colonoscopy audit from Gavin *et al.*[105] As no data were found to inform the probability of adverse events for flexible sigmoidoscopy, this was assumed to be the same as for colonoscopy, based on clinical expert opinion.

Costs

Price of tests and consultations were informed based on *NHS Reference Costs 2012–13*[106] and the Personal and Social Services Research Unit (PSSRU) 2013.[107] Costs on adverse events were also taken from *NHS Reference Costs 2012–13*.[106] The prices used for faecal occult blood testing and faecal immunochemical testing were estimated from the screening programme's Southern Hub 2011.[108] Lifetime costs for patients with CRC were taken from the Tappenden *et al.* study[99] and inflated to 2014 prices.

Utilities

The utilities that are associated with the different stages of cancer that were used in the model were obtained from Ness *et al.*,[95] although this paper assessed quality-of-life values in the USA using the standard gamble technique and its results were not valued in the UK. For healthy patients, utilities were taken from the Kind *et al.* study[96] [a large UK-based study on population health using the EuroQol-5 Dimensions (EQ-5D) survey]. No adjustment was made for age.

Analysis and interpretation of results

The study was generally well conducted, although details of which specific assays were considered to model faecal occult blood testing and faecal immunochemical testing were not reported, and the generalisability of findings was not discussed. In addition, faecal immunochemical testing was considered only in an additional analysis and not in the base case. The results showed that faecal immunochemical testing was cost-effective compared with colonoscopy, and, when all of the investigations were included, it remained cost-effective at a threshold of £20,000 per QALY. Given its recent date and UK setting, any parameter estimates included in this study were considered to be relevant for this assessment (see *Model structure and methodology*, below).

Other cost-effectiveness studies

The cost-effectiveness analysis in NG12[6] was largely based on the study by Allen *et al.*[109] However, this paper does not meet our inclusion criteria because faecal occult blood tests (FOBTs) were not considered in

the analysis (the study[109] investigated people with visible rectal bleeding and thus FOBTs were not relevant to this population). The cost-effectiveness of four diagnostic strategies (watchful waiting, flexible sigmoidoscopy, flexible sigmoidoscopy followed by air contrast barium enema, and colonoscopy) for patients with rectal bleeding was evaluated in this modelling study. The study was performed from a US-modified societal perspective. The authors concluded that colonoscopy was cost-effective compared with flexible sigmoidoscopy, with an ICER of US$5480 per QALY. Watchful waiting, defined as bleeding for 1 year followed by colonoscopy, was the most expensive strategy.

A second study, by Rae and Cleator,[110] was identified, which assessed the cost-effectiveness of the Hemoccult assay, the HO Sensa assay, the HemeSelect assay and a two-tier test combing HO Sensa and HemeSelect. Only HemeSelect is a FIT assay; this is a qualitative method and, therefore, does not meet our inclusion criteria. This study[110] was observational and its results showed that the costs per cancer detected were significantly lower for the two-tier test. Results were also presented for subgroups of asymptomatic and symptomatic patients. Symptomatic patients were defined as those who have:

- a personal history of ulcerative colitis, Crohn's disease or other IBDs, CRC, adenomas or polyps, *or*
- a family history of CRC or polyps, *or*
- one or more of the following symptoms: haemorrhoids, anal fissures, upper GI disease, diverticular disease, miscellaneous lower GI disease, or non-specific symptoms such as diarrhoea, nausea, bloating, fatigue, incontinence, visible blood in the faeces, melaena, weight loss, abdominal pain, anaemia, rectal pain, change in faeces calibre or change in bowel habits. This definition does not match the population specified for this assessment. The inclusion of people with a history or family history of cancer and the use of a qualitative FIT method mean that the study by Rae and Cleator[110] was considered to be of limited value for the current decision problem.

Although the studies by Allen *et al.*[109] and Rae and Cleator[110] did not meet our inclusion criteria, their characteristics are summarised in *Appendix 5*.

Model structure and methodology

A de novo health economic model was developed to explore the cost-effectiveness of using a quantitative FIT for Hb (occult blood) as a triage step in the investigation of symptomatic people presenting in the primary care who are at low risk of CRC, as defined in NG12.[1] The cost-effectiveness of faecal immunochemical testing was compared with both gFOBTs and no triage (referral straight to colonoscopy). The model consists of three parts: (1) a decision model reflecting the diagnosis of CRC; (2) a Markov state-transition model to estimate the long-term costs and effects [life-years (LYs) and QALYs] that are associated with the treatment and progression of CRC; and (3) a Markov state-transition model to estimate the LYs and QALYs that are associated with those who do not have CRC. Note that this second Markov model was not used to estimate costs because any differences in costs between the tests in those without CRC are assumed to occur only in the first year. The structure of the economic model used in this diagnostic assessment is similar to that used in NG12.[6] However, for some of the input parameters of our model, we could not find clear data from the literature. Thus, expert opinion was of key importance to the success of the model implementation. Therefore, we sent a questionnaire to 10 specialists; five of whom returned it, although not all questions were completely answered. The full questionnaire is included in *Appendix 6* (example questions included the percentage of patients who would eventually remain symptomatic after a positive FIT/gFOBT result and the plausible range for this percentage). The model used in the economic analyses of this diagnostic assessment is described, in detail, below.

Diagnostic model structure

The model begins with a cohort of symptomatic patients, presenting in primary care in whom referral to secondary care for investigation of possible CRC is being considered. A patient in the cohort is offered one of the following choices: faecal immunochemical testing, guaiac faecal occult blood testing or no triage

testing at all (referral straight to colonoscopy). A positive FIT or gFOBT results in referral to colonoscopy, whereas a negative test results in a watchful waiting strategy, in which a repeated test or further investigation can be performed when symptoms persist. Patients who had a FN gFOBT or FIT, and whose symptoms persisted, were assumed to receive a colonoscopy and thus be diagnosed within 1 year should they survive. Given the delay in diagnosis, it was also assumed that they would have an increased probability of progressing to a worse cancer state (i.e. these patients enter the CRC Markov model in a worse health state). This logically implies that no patients whose symptoms do not persist will have CRC, that is, all FIT-/gFOBT-negative patients who become asymptomatic do not have the target condition. These patients plus those found not to have CRC by colonoscopy were further modelled with a simple alive or dead Markov model, as described below (see *Healthy population Markov model*). Colonoscopy is considered to be the gold standard investigation for the diagnosis of CRC owing to its ability to visualise the entire colon and allow biopsies to be performed.[6] CTC is an alternative investigation of choice for people who are unfit for colonoscopy, but does not include biopsy.[6] For patients who test positive for CRC after colonoscopy or CTC, it was assumed that contrast-enhanced CT of the chest, abdomen and pelvis was performed, to determine the stage of disease. A time frame of 1 year was assumed for the diagnostic model. A schematic representation of the decision-analytic model is provided in *Figure 12*.

Colorectal cancer Markov model structure

The disease natural history used in the model was consistent with the existing UK-based screening economic models and divided the disease states by Dukes' grading (i.e. stage A – tumour confined to the mucosa; stage B – tumour infiltrating through muscle; stage C – lymph node metastases present; and stage D – distant metastases).[111] The structure of the Markov model was similar to the one used in NG12,[6] where cancer stages were defined based on the Dukes' grading system for CRC and then mapped into the health states of the Markov model. The initial distribution of patients with CRC through the model's health states was determined by the probability of being in a certain Dukes' stage. After the initial distribution of patients in the CRC model was determined, it was assumed that patients may stay in their current health state, progress to the health state representing the next worst stage of the condition or die (from CRC or another cause). A schematic representation of the CRC model is provided in *Figure 13*. A lifetime horizon with a 1-year cycle length captures the probability of progression for treated and untreated patients.

Healthy population Markov model

Colonoscopy is the reference standard used to determine the accuracy of quantitative FIT assays and guaiac faecal occult blood testing, for which CRC is the target condition. Thus, it was assumed that patients with a negative colonoscopy result do not have the target condition. It was also assumed that patients with the target condition will remain symptomatic; it therefore follows that all patients with a FN FIT or gFOBT result will remain symptomatic. All patients with a negative test result who become asymptomatic were assumed not to have the target condition.

Patients who do not have the target condition were further modelled with a simple alive or dead Markov model, as depicted in *Figure 14*. Survival estimates for this model were based on UK life tables.[98] Hence, patients entering this model can either die of any cause (including CRC, as a negative test result or a negative colonoscopy does not imply that these patients will never develop CRC) or stay in the alive health state. LYs and QALYs are accounted, but costs were not calculated in this model. This approach essentially implies two main assumptions for the difference in outcomes between intervention and comparator for those without CRC:

1. for life expectancy, this is caused only by a difference in mortality due to colonoscopy/CTC
2. for cost, this is due only to the difference in cost of guaiac faecal occult blood testing and colonoscopy/CTC.

This approach assumes that testing has no long-term (after 1 year) effect on costs or QALYs in disease-negative people and is consistent with our approach taken in previous NICE diagnostic assessments.[112] We have assumed that, in patients without CRC, faecal occult blood testing would not significantly delay

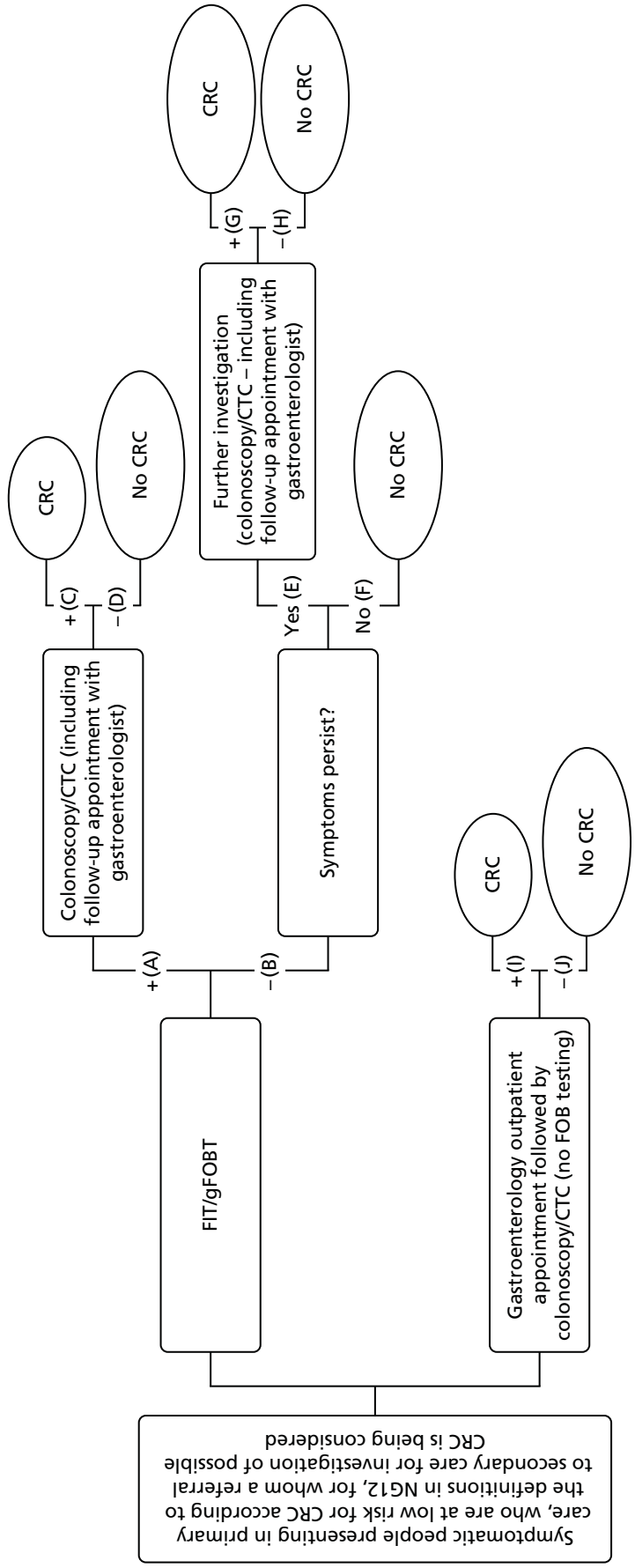

FIGURE 12 Diagnostic decision-analytic model.

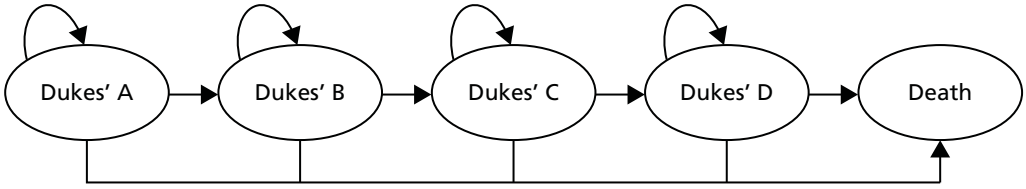

FIGURE 13 Colorectal cancer Markov model.

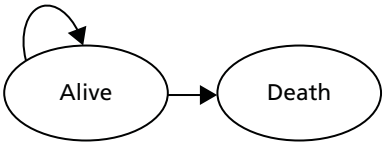

FIGURE 14 Healthy population Markov model.

diagnosis of the underlying cause of presenting symptoms and hence would not incur any extra cost or effect on mortality.

Model parameters

This section describes the input parameters used in the diagnostic model and in the Markov models and how their values were estimated for the base case.

Diagnostic model

Probabilities for faecal immunochemical testing and guaiac faecal occult blood testing diagnostic accuracy

Diagnostic accuracy was captured in the model using data on sensitivity and specificity that were obtained from our systematic review. For the base-case scenario, we considered a threshold of 10 µg Hb/g faeces or equivalent for the detection of CRC using a single faecal sample. This choice was based on the optimal threshold (maximum sensitivity and specificity) for each assay method and the threshold required to prove optimal rule-out performance (highest sensitivity and lowest number of cases missed), as explained in *Chapter 3* (see *Selection of test strategies for inclusion in cost-effectiveness modelling*). For this threshold and target condition, our systematic review obtained data only for OC-Sensor and HM-JACKarc. Therefore, the FOB Gold assay was not included in the base-case analysis. Pooled estimates for OC-Sensor (see *Table 6*) were obtained from the studies by McDonald *et al.*,[13] Mowat *et al.*,[52] Rodríguez-Alonso *et al.*[53] and Terhaar sive Droste *et al.*[58] Sensitivity and specificity for HM-JACKarc were obtained from Godber *et al.*[56] and are presented in *Table 11*. Finally, for guaiac faecal occult blood testing in the base-case scenario, we considered the sensitivity and specificity estimates used in NG12.[6] These estimates were reported by Gillberg *et al.*[91] This study[91] reports that the sensitivity of guaiac faecal occult blood testing is 75% and the specificity is 87%. However, in the NG12 economic model,[6] reported gFOBT sensitivity is 50% and the specificity is 88%. These figures were sourced from a subgroup of patients aged 41–50 years, because it was thought to better reflect the population considered in the NG12 economic model[6] (i.e. patients aged ≥ 40 years with a change in bowel habit as main symptom). Nevertheless, our systematic review identified two papers[92,93] reporting data on gFOBT accuracy, which are thought to represent a better match for the population specified for this diagnostic assessment. Therefore, additional scenarios, for which gFOBT accuracy data were based on these two studies,[92,93] were explored.

For the probabilistic sensitivity analysis (PSA), we assumed beta distributions for sensitivity and specificity. The parameters of the beta distributions used in the base-case scenario are summarised in *Table 23*. Technical details about the estimation of the parameters of the different probability distributions are given in *Appendix 10*. Several scenarios based on different assumptions for the accuracy of faecal immunochemical testing/guaiac faecal occult blood testing were explored. These are described below (see *Scenario analyses*).

TABLE 23 Sensitivity and specificity for OC-Sensor, HM-JACKarc and gFOBT, base case

Accuracy measure	OC-Sensor	HM-JACKarc	gFOBT
Sensitivity (95% CI)	92.1% (86.9% to 95.3%)	100% (71.5% to 100%)	50% (15.0% to 85.0%)
Probability distribution (parameters)	Beta (155.90, 13.45)	Beta[a] (1.16, 0.23)	Beta (2, 2)
Specificity (95% CI)	85.8% (78.3% to 91.0%)	76.6% (72.6% to 80.3%)	88% (85.0% to 89.0%)
Probability distribution (parameters)	Beta (100.80, 16.65)	Beta (380, 116)	Beta (962, 137)

a As FN = 0 in this case, sampling from a beta distribution with FN as a parameter will not work. A numerical approach was used to estimate the parameters shown here. The highest value of the mean for which the numerical approach converged was 0.98. Therefore, this value was chosen as the mean value for the PSA. The 95% CI (71.5% to 100%) was reproduced exactly. The median was 100%.

Our model also requires the calculation of the probability of having the condition or not, contingent on the test performance. When the disease prevalence is known, sensitivity and specificity can be used to calculate the PPVs and negative predictive values (NPVs) using the formulae below:

$$\text{PPV} = \frac{\text{sensitivity} \times \text{prevalence}}{(\text{sensitivity} \times \text{prevalence}) + [(1 - \text{specificity}) \times (1 - \text{prevalence})]} \quad (1)$$

and

$$\text{NPV} = \frac{\text{specificity} \times (1 - \text{prevalence})}{[(1 - \text{sensitivity}) \times \text{prevalence}) + (\text{specificity} \times (1 - \text{prevalence})]}. \quad (2)$$

The prevalence of CRC in the base-case population was assumed to be 1.5%, the same as in NG12.[6] For the PSA, we assumed a triangular distribution of between 1% and 2%. The results of our systematic review showed that, for a threshold 10 µg Hb/g faeces or equivalent, and CRC as target condition, prevalence ranges between 2.1% and 5.4%. Therefore, the impact of this assumption on the cost-effectiveness results was explored with additional scenario analyses, for which the most likely value for the prevalence was assumed to be 3% and 5.4%, and with an additional scenario for which we used a triangular distribution with, most likely, a value of 1.5% and limits of 1% and 5.4% in the PSA.

Assuming that the prevalence of CRC in the base-case population is 1.5%, PPV and NPV estimates were calculated. Whereas the PPV was directly used as a node probability in the model (the probability labelled 'C' in *Figure 12*), the NPV was included in the model in the calculation of the probability that CRC is present for symptomatic patients after a negative FIT/gFOBT (the probability labelled 'G' in *Figure 12*). Details for probability ('G') are given below. PPV and NPV estimates for the base-case scenario are summarised in *Table 24*.

TABLE 24 The PPV and NPV for OC-Sensor, HM-JACKarc and gFOBT, base case

Accuracy measure	OC-Sensor (%)	HM-JACKarc (%)	gFOBT (%)
PPV	8.9	6.1	5.7
NPV	99.8	100	99.1

Probability of remaining symptomatic after a negative test result

The model assumes that only those patients with a negative test result, and whose symptoms do not persist, do not receive a colonoscopy/CTC. Therefore, it is for this group of patients that most of the savings in costs are expected, when the test strategies are compared with no triage (referral straight to colonoscopy). We did not identify any data, from the literature, on the proportion of patients with a negative faecal occult blood test result in whom symptoms will persist and who will eventually receive a colonoscopy/CTC. This information was therefore derived from clinical expert opinion, using the questionnaire described previously. In the questionnaire, we asked what percentage of patients who test negative with faecal immunochemical testing/guaiac faecal occult blood testing would persist in their symptoms and eventually undergo colonoscopy, and the plausible range for this percentage. In addition, we asked for the percentage of patients who would receive a second FIT/gFOBT. The responses to these two questions are presented in *Table 25*. It is essential to note that a second FIT/gFOBT is not considered to be a replacement for a colonoscopy, given that only the latter is diagnostic. Ideally, we would have liked to estimate the percentage of patients who get a colonoscopy that is contingent on the result of the second FIT/gFOBT, but the data on accuracy of repeat test were unavailable and it was believed that accuracy could not be adequately estimated by clinical experts. Therefore, in our model, having a second FIT/gFOBT increases the costs of only 20% (see *Table 25*) of the patients who, after testing negative, will remain symptomatic. The impact of this assumption on the cost-effectiveness results was explored in an additional scenario.

We assumed that the percentages of test-negative patients who undergo colonoscopy and the percentages who get a repeat FIT/gFOBT follow a triangular distribution, with the point estimate given by the experts representing the mode of the distribution. After simulating from these triangular distributions, we were able to estimate the pooled means and standard deviations (SDs) of the aforementioned probabilities, which are further assumed to have beta distributions. For the probability of undergoing colonoscopy after a negative result we found a mean of 32.5% and a SD of 7.3%, whereas for the mean probability and SD of getting a second FOB test were 20% and 3.2%, respectively.

Probability that colorectal cancer is present for symptomatic patients after a negative faecal immunochemical test/guaiac faecal occult blood test

This is the probability labelled 'G' in *Figure 12*. This probability can be calculated as '(1 – NPV)', divided by the probability of remaining symptomatic after a negative test result (the latter probability was estimated by clinical experts as explained above); details of calculations are provided in *Appendix 7*. Defining 'G' as a quotient and having the probability of remaining symptomatic after a negative test result in the denominator, which is assumed to follow a beta distribution, may cause numerical problems when performing a PSA (numerical division by 0). Therefore, for the PSA, we assumed that the probability of

TABLE 25 Percentage of test negative patients who remain symptomatic (and undergo colonoscopy) or get a second test, per expert

Expert	% of patients who remain symptomatic (undergo colonoscopy)	Lowest (%)	Highest (%)	% of patients who get second FIT/gFOBT	Lowest (%)	Highest (%)
1	55	30	80	30	20	40
2	10	5	15	10	5	15
Mode (pooled average)	32.5%	–	–	20	–	–
SD	7.3	–	–	3.2	–	–
Parameters beta distribution	$\alpha = 13.05$; $\beta = 27.11$	–	–	$\alpha = 31.05$; $\beta = 124.20$	–	–

SD, standard deviation.

remaining symptomatic after a negative test result was fixed to its mean value (0.325). The estimated probability 'G' for the base-case scenario is summarised in *Table 26*.

Table 27 shows a summary of the probabilities used at the decision nodes in the diagnostic model. These were labelled as 'A' to 'J' in *Figure 12*. Full derivations of the equations are provided in *Appendix 7*.

TABLE 26 Probability that CRC is present for symptomatic patients after negative FIT/gFOBT for OC-Sensor, HM-JACKarc and gFOBT, base case

Accuracy measure	OC-Sensor	HM-JACKarc	gFOBT
Probability (%) that CRC present for symptomatic patients after negative FIT/gFOBT	0.4	0	2.65

TABLE 27 Probabilities at decision nodes in the diagnostic model

Label	Definition	Formula	Base-case value (%)
A	Probability that FIT/gFOBT is positive	(sensitivity × prevalence) + [(1 – specificity) × (1 – prevalence)]	OC-Sensor = 15.35 HM-JACKarc = 24.53 gFOBT = 13.02
B	Probability that FIT/gFOBT is negative	1 – (A)	OC-Sensor = 84.65 HM-JACKarc = 75.47 gFOBT = 86.98
C	Probability that CRC is present after a positive FIT/gFOBT	PPV	OC-Sensor = 8.99 HM-JACKarc = 6.11 gFOBT = 5.75
D	Probability that CRC is not present after a positive FIT/gFOBT	1 – PPV	OC-Sensor = 91.01 HM-JACKarc = 93.89 gFOBT = 94.25
E	Probability that symptoms persist after a negative FIT/gFOBT	NA – based on expert opinion	32.50
F	Probability that symptoms do not persist after a negative FIT/gFOBT	1 – (E)	67.50
G	Probability that CRC is present for symptomatic patients after a negative FIT/gFOBT	(1 – NPV)/(E)	OC-Sensor = 0.43 HM-JACKarc = 0 gFOBT = 2.65
H	Probability that CRC is not present for symptomatic patients after a negative test	1 – (G)	OC-Sensor = 99.57 HM-JACKarc = 100 gFOBT = 97.35
I	Probability that CRC is present	Prevalence	1.5
J	Probability that CRC is not present	1 – (I)	98.5

NA, not applicable.

Probability of being referred to colonoscopy or CTC after a positive test result:

If the gFOBT or FIT result is positive, patients are referred to either colonoscopy or CTC. To estimate the percentage of patients who are referred to each of these options in the UK, we also relied on expert opinion. The responses to this question are presented in *Table 28*.

We adopted the approach described above for estimating the probability of remaining symptomatic after having a negative test result. In this case, for the probability of being referred to colonoscopy versus CTC after a positive test result we calculated a mean of 88.3% and a SD of 1.49%. The impact of this assumption was explored in an additional scenario.

Probability of adverse events associated with colonoscopy

Our diagnostic model considers the probability of experiencing adverse events that are associated with colonoscopy. The economic model presented in the NG12[6] was used as a starting point for selecting the adverse events to be included. The economic model in NG12[6] includes two adverse events that are related to colonoscopy: bowel perforation and bleeding. Probability data for these adverse events were obtained from Gavin *et al.*[105] This study was a 2-week audit, performed in the UK, which provided data on colonoscopy completion rates and associated adverse events.

A literature search was performed to assess whether or not the adverse events and associated probabilities used in NG12[6] were complete and still appropriate for the current decision problem. Our search identified five potentially relevant studies.[113–117] These were four reviews[113–116] and one population-based study.[117] Two of the reviews, by Manta *et al.*[115] and Church,[116] were overviews that did not include a systematic approach to searching literature; neither did these reviews include further analysis. The two other reviews, by Reumkens *et al.*[113] and Day *et al.*,[114] were systematic literature reviews and both included a meta-analysis. The review by Day *et al.*[114] studied adverse events in elderly patients who were undergoing colonoscopy. Elderly patients were defined as those who were ≥ 65 years of age. Therefore, this study[114] was of limited relevance to the population that was specified for this assessment. The review by Reumkens *et al.*[113] studied post-colonoscopy complications in population-based studies. It is a very recent systematic review; it provides estimates of adverse events rates, including CIs, and is not limited to a specific patient population. The estimates provided for bowel perforation and bleeding are very similar to those in Gavin *et al.*,[105] which were the ones used in the cost-effectiveness analysis performed in NG12.[6] The studies by Gavin *et al.*[105] and Saraste *et al.*[18] were population-based studies. These were deemed to be of less relevance, as systematic literature reviews are preferred over single studies. Therefore, the study by Reumkens *et al.*[113] was deemed to be the most appropriate study to populate the probability of adverse events due to colonoscopy in the diagnostic model. The adverse events included in the model are bowel bleeding, perforation and death.

TABLE 28 Percentage of test positive patients who are referred to colonoscopy vs. CTC, per expert

Expert	% of patients referred to colonoscopy	Lowest	Highest
1	75	NR	NR
2	95	90	100
3	93	NR	NR
4	90	85	95
Mean (pooled)	88.3	–	–
SD	1.49	–	–
Parameters beta distribution	$\alpha = 417.40$; $\beta = 55.81$	–	–

NR, not reported.

The corresponding probabilities and the parameters of a beta distribution used for the PSA are presented in *Table 29*.

The probabilities of experiencing adverse events due to CTC are scarce in the literature. The study of Burling *et al.*[118] found that the proportion of patients with symptomatic perforation that was attributable to CTC was 0.03% but none of these was classified as a serious adverse event. The same article states that perforation rates for colonoscopy are four times higher than for CTC. No death events were reported and the proportion of patients experiencing bleeding after examination was not described in this study. Owing to the uncertainty around these parameters and in order to keep the model simpler, we assumed that, in the base-case scenario, adverse event rates due to CTC were the same as those of colonoscopy. Give that this assumption will result in an overestimation, it can be interpreted as a worst-case scenario regarding the total number of adverse events. In addition, as, on average, only 11.7% of the patients receive CTC (as opposed to colonoscopy) the impact of this assumption is expected to be very small. We explored the impact of this assumption on the cost-effectiveness results by performing additional scenario analyses.

Costs

Direct costs included in the model are test costs, costs of colonoscopy/CTC, adverse event costs and CT costs. Indirect costs parameters were not included in the model, given the perspective of the NHS.

Test costs

Faecal immunochemical testing and guaiac faecal occult blood testing cost estimates reported in the literature vary quite significantly, and the assumptions made to derive those estimates are not clear in the majority of cases. Therefore, in this section we present the cost estimates used in this diagnostic assessment and the underlying assumptions leading to them. At the end of this section, several test costs from different sources are compared (see *Table 33*).

Faecal immunochemical test To estimate the total costs of a FIT, we assumed that these include the following subcategories: costs of the collection device, acquisition costs of the analyser, cost of materials to analyse the collected sample (i.e. reagents, buffer, reaction cells, bottles) and costs of maintenance of the analyser. The manufacturers were the only source of unit costs. Training costs and the costs of the laboratory staff for analysing the test results were not included in the total costs because it was assumed that these costs are the same for faecal immunochemical testing and guaiac faecal occult blood testing, and, therefore, these costs have no impact on the incremental cost-effectiveness results when these two alternatives are compared.

Costs of the collection device For both the FIT and gFOBT, a faecal sample from the patient is required. The patient has to collect the sample at home. The collection device is an instrument, designed for patient use, to collect the sample in a hygienic and easy way. Generally, the device consists of a vessel that contains a buffer and a probe to collect the faecal sample.[119]

Acquisition costs of analyser Resource use data are needed to estimate the acquisition costs of the FIT analysers. The report from the Association of Coloproctologists of Great Britain and Ireland 2015[120] suggests that, for a population of 500,000, up to 6000 colonoscopies and 4000 flexible sigmoidoscopies

TABLE 29 Probability of experiencing adverse events due to colonoscopy

Adverse event	Rate % (95% CI)	Beta distribution parameters	Source
Bleeding	0.26 (0.17 to 0.37)	$\alpha = 25.82$; $\beta = 9887.90$	Reumkens 2016[113]
Perforation	0.05 (0.04 to 0.07)	$\alpha = 49.52$; $\beta = 91{,}719.86$	
Death	0.0029 (0.0011 to 0.0055)	$\alpha = 6.40$; $\beta = 222{,}513$	

will be needed annually if international comparisons and trends are followed. These figures were also validated by expert opinion. Therefore, it was assumed that 10,000 colonoscopies would be required to deal with referrals from primary care per 500,000 people. Assuming that there is one laboratory per 500,000 people and that 10,000 requests for faecal immunochemical testing are made each year (at 253 'working days' per annum) would imply that approximately 40 requests would be received each day. Thus, only one analytical system would be needed, which would be run for only a short period of time. In order to have the minimal turnaround time that is a prerequisite for such a service, the analyser would need to be run each day. For the acquisition costs of the analyser, we considered the prices provided by the manufacturers (list pricing based on the capital purchase of an instrument). As the time frame for the diagnostic part of the health economic model is 1 year, the total cost of the analyser was used. A summary of the estimated resource is presented in *Table 30*.

Costs of reagents Material costs include costs of the reagents, buffer, reaction cells and analyser cups. For OC-Sensor, the manufacturer provided prices for only the reagents (£0.80). Therefore, it was assumed that this price also includes the costs of buffers and other consumables. The manufacturer of HM-JACKarc provided information on all of the materials. The costs of the buffers and reaction cells were given per package. These were converted to costs per test.

Costs for maintenance of the analyser Maintenance costs include costs of calibration, costs of daily controls, service costs and costs for cleaning the analyser. For OC-Sensor, only the costs of a calibration kit and costs of daily controls were provided by the manufacturer. The costs of the calibration kit were given per half-year for OC-Sensor. No information about calibration costs was provided for HM-JACKarc. The manufacturer of OC-Sensor recommends that, before the analysis of samples, a single high and a single low control should be analysed, that is, one low test and one high test per day. This information was not provided for HM-JACKarc, and hence we assumed that it was the same. Finally, the cost of washing material was provided only for HM-JACKarc.

Guaiac faecal occult blood test Costs of guaiac faecal occult blood testing were obtained from the literature and from clinical experts. Estimates found in the literature range from (confidential information has been removed) up to £9.57 per gFOBT. However, in most cases it is not clearly reported how the costs were estimated. For those reasons, the cost estimate provided by clinical experts was chosen for the base-case scenario. A summary of the different cost estimates for guaiac faecal occult blood testing considered in this diagnostic assessment is given in *Table 31*.

Table 32 presents the estimated costs for the OC-Sensor and the HM-JACKarc FIT assays. The information provided by the manufacturer did not allow the cost of the FOB Gold system to be estimated in detail, hence FOB Gold is not included in *Table 32*; total cost is provided in *Table 33*.

A summary of the different cost estimates for faecal immunochemical testing that have been considered in this diagnostic assessment and compared with the literature/other sources can found in *Table 33*.

TABLE 30 Estimated resource use

Resource use[a]	
Average daily workload, UK	40
No. of samples analysed per year	10,000
No. of machines required to analyse daily workload (per year)	1

a Personal communication (e-mail from Callum Fraser, NHS Tayside, to Marie Westwood, KSR Ltd, 19 July 2016).

TABLE 31 Comparison of gFOBT cost estimates

Total cost per test (£)	Source
0.7758[a]	Personal communication: e-mail from Callum Fraser, 19 July 2016
(Confidential information has been removed)	Personal communication: e-mail from Jacqueline Murphy, 21 July 2016
9.57[b]	Sharp 2012[122]
1.46[c]	Whyte 2011[123]
4.86	NG12[6]

a Includes only gFOBT kit (device, spatula, envelope and reagents).
b Inflated to 2015 prices and converted into UK pounds (reported in €): £1.71 kit, £7.86 processing and analysis.
c Includes gFOBT kit (device, spatula, envelope and reagents) £0.46, and processing costs (per test) £0.78, further inflated to 2015 prices (£0.54 and £0.92, respectively).

TABLE 32 Costs of faecal immunochemical testing

Cost item	OC-Sensor (£)	HM-JACKarc (£)
Test costs		
Reagents	0.80	0.49
Sample device	1.30	2.10
Total costs per test	2.10	2.59
Material costs		
Measurement device (per year)	19,061.00	22,458.00
Measurement materials (per year)		
Bottles	NR	910.40[a]
Analyser control cups	40.00[b]	NR
Maintenance (per year)		
Service costs	NR	0.00
Auto washer	NR	10.18[c]
Calibration kit	1200.00[d]	NR
Daily controls[e]	4048.00	11,134.53
Total costs of device and maintenance (per year)	24,349.00	34,513.11
Material cost per test	2.43	3.45
Total costs		
Total cost per test (including material costs)	4.53	6.04

NR, not reported.
a £45.52 for 500 pieces, so £45.52 × (10,000/500).
b Cost for 1000 cups (one per year/laboratory).
c £30.55 for 200 ml, so £30.55 × (10,000/30,000).
d One hundred kits per month.
e Assume four controls per day: one high and one low and two more for calibration. Then it is 253 × 4 = 1012 per year. £4 and £11 per control/calibration for OC-Sensor and HM-JACKarc, respectively.

TABLE 33 Comparison of FIT cost estimates

FIT assay	Total cost per test (£)	Source
OC-Sensor	4.53	This diagnostic assessment
HM-JACKarc	6.04	This diagnostic assessment
FOB Gold	1.96	This diagnostic assessment
NR	2.15[a]	Grazinni 2008[121]
NR	10.23[b]	Sharp 2012[122]
NR	9.42[c]	NG12[6]
NR	3.63	Whyte 2011[123]
NR	(Confidential information has been removed)	Personal communication [e-mail from Jacqueline Murphy, Health Economics Research Centre (HERC), Nuffield Department of Population Health, University of Oxford, to Marie Westwood, KSR Ltd, 21 July 2016]

NR, not reported.
a Includes costs of FIT kit, reagents and consumables separately.
b Includes subtotal cost of kit plus consumables and processing costs (although it is unclear how the latter were estimated).
c Not mentioned how these were estimated.

Other costs included in the diagnostic model

Estimates of the costs of colonoscopy, CTC and CT were obtained from the *NHS Reference Costs 2014–15*.[124] We estimated the costs of colonoscopy as the average cost of diagnostic colonoscopy (for adults aged ≥ 19 years) with and without biopsy, because, as stated in NG12,[6] a biopsy may be taken during the colonoscopy investigation. For the CTC costs, we followed the approach by Halligan *et al.*[104] and, in the absence of a specific UK national cost for CTC, we used the cost of CT (more than three areas) as an approximation. Finally, to estimate the CT costs, we calculated the average of all of the CT procedures that were available for adults, that is, CT of one, two, three or more areas with or without (pre and/or post) contrast and complex CT [Healthcare Resource Group (HRG) codes RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z and RD28Z – Outpatient department].

Costs associated with GP and gastroenterology outpatient appointments were also considered in the model. In particular, we assumed that the cost of colonoscopy/CTC includes the costs of a follow-up appointment with a gastroenterologist. The definition of our patient population, as symptomatic people presenting in the primary care who are at low risk of CRC, implies that patients have already visited the GP (and therefore these costs have been incurred) before entering the model. Only for test-negative patients whose symptoms persist were additional GP appointment costs considered.

Costs of bleeding and perforation were estimated based on the average length of hospital stay that was associated with each of these adverse events. Average length of stay was obtained from the study of Gavin *et al.*[105] The average length of stay for bleeding due to colonoscopy was 1.7 days and for perforation 9.1 days. To estimate the total costs, these were multiplied by the NHS cost of a regular day or night admission.

All of these costs (with the input parameters used in the PSA) are summarised in *Table 34*.

Utilities

No evidence was found on the effects of bleeding and perforation on quality of life. Thus, in line with the cost-effectiveness analysis performed in NG12,[6] our diagnostic model did not include disutilities for adverse events. In addition, as these events are often of short duration, the effects on quality of life can be assumed to be negligible. Therefore, the only utilities that were considered in our diagnostic model were those associated with the different stages of cancer (from Ness *et al.*[95]) and the general population sex- and age-related utilities for healthy patients (from Kind *et al.*[96]). These utilities are described in detail below.

TABLE 34 Costs included in the diagnostic model

Type of cost	Mean cost (£)	Gamma distribution parameters	HRG codes	Source
Investigation				
Diagnostic colonoscopy	372	(4.12, 90.15)	Average of FZ51Z (Diagnostic Colonoscopy, 19 years and over) and FZ52Z (with biopsy) – Outpatient procedures (Gastroenterology)	*NHS Reference Costs 2014–15*[124]
CTC	136	(9.18, 14.80)	RD27Z (Computerised Tomography Scan of more than three areas) – Outpatient department	Halligan 2015[104] and *NHS Reference Costs 2014–15*[124]
CT	116	(7.56, 15.32)	Average of RD20A, RD21A, RD22Z, RD23Z, RD24Z, RD25Z, RD26Z, RD27Z and RD28Z – Outpatient department	*NHS Reference Costs 2014–15*[124]
Referral				
GP visit	44	NA	NA	PSSRU 2015 – table 10.8b[125]
Gastroenterology outpatient appointment	135	(9.02, 14.97)[a]	Total outpatient attendances – Gastroenterology (Service code 301)	*NHS Reference Costs 2014–15*[124]
Adverse event				
Bleeding	603	(9.02, 66.78)[a]	RP (Regular Day or Night Admissions) – £354.67; average length of stay 1.7 days	Gavin 2012[105] and *NHS Reference Costs 2014–15*[124]
Perforation	3228	(9.02, 357.47)[a]	RP (Regular Day or Night Admissions) – £354.67; average length of stay 9.1 days	Gavin 2012[105] and *NHS Reference Costs 2014–15*[124]
Death	0	NA		Assumption

NA, not applicable.
a Parameters not reported. Calculated assuming 20% deviation from the mean.

Colorectal cancer Markov model

Initial distribution of patients per Dukes' stage

The initial distribution of patients with CRC over the model's health states was determined by the probability of being in a certain Dukes' stage at diagnosis. In NG12,[6] this was estimated using data from the NCIN,[98] which showed the percentage of patients in England diagnosed at each stage of CRC between 1996 and 2002. The reported percentages per Dukes' stage were 13%, 37%, 36% and 14% for stages A–D, respectively, for 202,694 patients. The paper by Cubiella *et al.*,[55] included in our systematic review (see *Chapter 3*, *Diagnostic performance of the OC-Sensor faecal immunochemical test assay*), also reported the sensitivity of OC-Sensor for determining the stage and location of CRC using a single faecal sample when a threshold of ≥ 20 µg Hb/g faeces is considered. The total number of patients with CRC in this study was 91, and the percentages per stages A–D were 16%, 25%, 44% and 14%, respectively. We also consulted about this with our clinical experts and the percentages (average between four experts) per stages A–D were 19%, 35%, 32%, and 15%, respectively. All of these values are summarised in *Table 35*. For the base-case scenario, we considered the estimates from NCIN as in NG12.[6] The main reasons were that the sample size used to obtain these estimates is large in NCIN and data were obtained from UK population; therefore, the estimated percentages can be considered more reliable than those in Cubiella *et al.*[55] In addition, estimates derived from NCIN were similar to those provided by clinical experts who answered our questionnaire.

TABLE 35 Number of cases (percentage) per stage at diagnosis of patients with CRC

Dukes' stage				
A	B	C	D	Source
26,727 (13%)	74,784 (37%)	72,806 (36%)	28,377 (14%)	Patients diagnosed between 1996 and 2002, England (NICN)[98]
15 (16%)	23 (25%)	40 (44%)	13 (14%)	Cubiella 2014 (COLONPREDICT)[55]
38,512 (19%)	70,943 (35%)	64,862 (32%)	30,404 (15%)	Expert opinion and assuming total figure in NCIN

Probability of progression

The probability of progression was modelled as in NG12.[6] In the clinical guideline, it was noted that obtaining observed probabilities of progression for the patient population considered was unlikely. Therefore, in the absence of such evidence, the probability of progression was estimated using progression probabilities for *undiagnosed* patients with CRC, which were obtained from Tappenden *et al.*[99] The uncertainty within the model results resulting from this assumption was explored in the sensitivity analysis. The progression probabilities used in the model are presented in *Table 36*.

Delayed diagnosis

Our model assumes that patients who had a FN gFOBT/FIT, and whose symptoms persisted, have an increased probability of progressing to a worse cancer state, given the delay in diagnosis. This was implemented in the model by shifting the initial distribution of patients per Dukes' stages in *Table 35* according to the progression probabilities shown in *Table 36*. Note that, for the base-case scenario, the initial proportions of patients per Dukes' stage were 13% (A), 37% (B), 36% (C) and 14% (D). Using the annual progression probabilities for undiagnosed patients with CRC in *Table 36*, that is, assuming a delay of 1 year, the proportions of patients per Dukes' stage were estimated as 6% (A), 20% (B), 29% (C) and 45% (D). However, it was assumed that FN patients would persist in their symptoms and they would be diagnosed within 1 year by colonoscopy or CTC. Therefore, it seems reasonable to assume that a delay of 1 year would overestimate the time to delayed diagnosis. For that reason, we assumed a delay of 6 months for the base-case scenario. The probabilities of progression between Dukes' stages at 6 months were calculated by halving those in *Table 36* (0.29 from A to B, 0.33 from B to C and 0.435 from C to D). This method implicitly assumes a uniform distribution of yearly progression probabilities. Assuming a delay of 6 months, the proportions of patients per Dukes' stage were estimated as 9% (A), 29% (B), 32% (C) and 30% (D). A summary of the number of cases per stage, with and without delay in diagnosis, are presented in *Table 37*. In the PSA, this was modelled as a Dirichlet distribution, with the number of cases as the parameters of the probability distribution.

TABLE 36 Probability of progression for undiagnosed CRC

CRC Dukes' stage transition	Annual progression probability – undiagnosed CRC (95% CI)	PSA distribution	Source
A to B	0.58 (0.57 to 0.59)	Uniform	Tappenden 2007[99]
B to C	0.66 (0.64 to 0.67)		
C to D	0.87 (0.85 to 0.88)		

TABLE 37 Number of cases (percentage) per stage at 'initial', 'delayed 6 months' and 'delayed 1 year' diagnosis of patients with CRC

	Dukes' stage			
Number of cases	A	B	C	D
Initial	26,727 (13%)	74,784 (37%)	72,806 (36%)	28,377 (14%)
Delayed 6 months	18,976 (9%)	57,856 (29%)	65,814 (32%)	60,048 (30%)
Delayed 1 year	11,225 (6%)	40,928 (20%)	58,822 (29%)	91,718 (45%)

Survival probability per Dukes' stage

Disease-specific mortality was also estimated using data from the NCIN, with the reported 5-year survival rates used as a starting point for extrapolation.[98] *Tables 38* and *39* show the 5-year survival probabilities with 95% CIs at each Dukes' stage, and the observed survival probabilities at each year per Dukes' stage, from NCIN data, respectively.[98]

It was not possible to properly extrapolate survival curves beyond year 5 using these data. We therefore used available 15-year predicted survival data from NG12[6] (e-mail from Matthew Prettyjohns, National Collaborating Centre for Cancer, Cardiff, to Marie Westwood, KSR Ltd, 7 July 2016, personal communication) to model CRC survival/mortality in the 15 first cycles of the CRC Markov model. These probabilities are shown in *Appendix 8*. Furthermore, we assumed that, after year 15, CRC-related mortality remains constant. However, overall mortality increases after year 15 owing to the inclusion of age-specific mortality based on UK life tables.[98] The annual mortality estimates and the parameters of beta distributions used in the PSA are also shown in *Appendix 8*. Finally, we used two different data sources for the transition probabilities: annual mortality per Dukes' stage and annual progression (for undiagnosed patients) between Dukes' stages separately. To accommodate these two data sets in the CRC model,

TABLE 38 Five-year relative survival of patients with CRC diagnosed between 1996 and 2002, England (NCIN)

Stage at diagnosis	5-year relative survival (%)	95% CI
Dukes' A	93.20	92.5 to 93.9
Dukes' B	77.00	76.4 to 77.5
Dukes' C	47.70	47.1 to 48.3
Dukes' D	6.60	6.1 to 7.0

TABLE 39 Yearly CRC survival per Dukes' stage, England (NCIN)[a]

	Stage observed			
Year	Dukes' A	Dukes' B	Dukes' C	Dukes' D
0	100	100	100	100
1	96.68	91.17	80.67	37.39
2	96.11	86.74	67.06	18.55
3	95.22	82.50	57.56	11.03
4	94.17	78.94	51.12	8.07
5	92.64	76.29	46.87	6.43

a Personal communication: e-mail from Matthew Prettyjohns, National Collaborating Centre for Cancer, Cardiff, to Marie Westwood, KSR Ltd, 7 July 2016.

we assumed that transitions between the states of the model occurred in two steps. First we calculated the number of patients dying per cycle and then, conditional on survival, we calculated progression between Dukes' stages. The implications of these assumptions were explored in the sensitivity analysis, and further discussed in *Chapter 5* of this report.

Costs

Estimated total costs were collected over the modelled lifetime horizon. The costs considered in the model reflect those that are relevant to the NHS and Personal Social Services. The total costs include initial and follow-up investigations, staging, treatment, drug costs and any other resource use that may be required (e.g. GP visit). All of the costs were taken from NG12.[6] Data on lifetime costs associated with CRC (based on the stage of cancer at diagnosis) were sourced from Tappenden *et al.*[99] and inflated to 2015 prices using the 2014/15 Hospital and Community Health Services index available from the PSSRU.[125] All of the costs applied in the model are shown in the *Table 40*. The costs associated with the health states of the CRC Markov model were estimated as lifetime costs (i.e. one-off cost). To properly account for discounting, it is necessary to calculate costs for each cycle of the Markov model (i.e. costs per year) in order to apply the corresponding discount rate per year. We assume that these lifetime costs are uniformly distributed over the model's time horizon. It can be argued that this assumption may not reflect accurately the distribution per year of lifetime costs. However, given the low CRC prevalence in the patient population, this assumption is expected to have little impact on the model results.

Utilities

Health benefits were expressed in terms of LYs and QALYs (QALYs) gained. QALYs were estimated by combining the LY estimates, with utility values associated, with being in a particular health state of the CRC model. These utility values were sourced from the Ness *et al.* study[95] and were also used in the cost-effectiveness model developed for NG12.[6] The study by Ness *et al.*[95] concluded that factors such as age and sex were not significant predictors for any utility value. Therefore, the utilities applied in the model are dependent only on the CRC stage and remain constant for all model cycles. The utilities included in the CRC Markov are presented in *Table 41*.

TABLE 40 Lifetime CRC costs included in the model

Cancer stage	Mean cost, £ (SE)	Gamma distribution parameters (α, β)[a]	Source
Dukes' A	10,681 (3959)	(7.28, 1467.43)	Tappenden 2007[99] (inflated to 2015)
Dukes' B	18,011 (6676)	(7.28, 2474.54)	
Dukes' C	29,139 (10,800)	(7.28, 4002.88)	
Dukes' D	19,391 (7187)	(7.28, 2663.76)	

SE, standard error.
a Note: $\alpha = (\text{mean}/\text{SE})^2$; $\beta = \text{SE}^2/\text{mean}$.

TABLE 41 Utilities included in the CRC Markov model

Model state	QoL	Beta distribution (alpha, beta)	Source
Dukes' A	0.74	(145.00, 51.69)	Ness 1999[95]
Dukes' B	0.70	(56.60, 24.53)	
Dukes' C	0.50	(33.78, 32.28)	
Dukes' D	0.25	(1.03, 2.35)	

QoL, quality of life.

Healthy population Markov model

This model accounted only for LYs and QALYs accrued on a healthy health state over a lifetime. Age- and sex-specific all-cause mortality estimates were based on UK life tables.[98] In particular, we assumed, for the base-case scenario, patients aged ≥ 40 years, as in NG12.[6] For the proportion of female patients, we used the figures reported in the Gillberg *et al.* study,[91] in which 715 females and 388 males were included. Mortality estimates, and the corresponding parameters of a beta distribution for the PSA, can be found in *Appendix 9*. Utilities were sourced from Kind *et al.*[96] Unlike in NG12,[6] for which only a mean utility value equal to 0.79 was considered for all healthy patients, we included sex- and age-related utilities for every cycle of the Markov model. These were calculated as a weighted average, using the proportion of females reported in Gillberg *et al.*[91] (35% male, 65% female). These utilities are presented in *Table 42*.

Overview of main model assumptions

Table 43 summarises the main assumptions made in our economic model.

TABLE 42 Age-specific utilities based on the general UK population that was included in the healthy population Markov model

Age (years)		Weighted average	Males	Females
35–44	Mean	0.91	0.91	0.91
	SD	0.11	0.17	0.15
	Beta (α, β)	(5.24, 0.51)	–	–
45–54	Mean	0.85	0.84	0.85
	SD	0.18	0.27	0.23
	Beta (α, β)	(2.49, 0.44)	–	–
55–64	Mean	0.80	0.78	0.81
	SD	0.20	0.28	0.26
	Beta (α, β)	(2.40, 0.60)	–	–
65–74	Mean	0.78	0.78	0.78
	SD	0.19	0.28	0.25
	Beta (α, β)	(2.92, 0.82)	–	–
≥ 75	Mean	0.72	0.75	0.71
	SD	0.20	0.28	0.27
	Beta (α, β)	(2.90, 1.13)	–	–

TABLE 43 Main model assumptions

General	Source
1. It was assumed that a lifetime horizon with a 1-year cycle length captures the probability of progression for treated and untreated patients	Assumption/NG12[6]
2. Any differences in costs between the tests in patients without CRC were assumed to occur only in the first year	Assumption
3. Any differences in life expectancy between intervention and comparator for patients without CRC are due only to the difference in mortality due to colonoscopy/CTC	
4. Any differences in costs between intervention and comparator for patients without CRC are only due to difference in cost of guaiac faecal occult blood testing and colonoscopy/CTC	
5. Testing has no long-term (after 1 year) effect on costs or QALYs in disease-negative people. Thus, in patients without CRC, faecal occult blood testing would not significantly delay diagnosis of the underlying cause of presenting symptoms and hence would not incur any extra cost or effect on mortality	

continued

TABLE 43 Main model assumptions (*continued*)

General	Source
Diagnostic model	
6. A time frame of 1 year was assumed for the diagnostic model	NG12[6]/expert opinion
7. A positive FIT/gFOBT results in referral to colonoscopy	
8. A negative FIT or gFOBT results in a watchful waiting strategy, in which a colonoscopy/CTC will be performed when symptoms persist. A repeat FIT/gFOBT might also be performed, but referral to colonoscopy/CTC is not modelled as being contingent on the results of the repeat test	
9. The sensitivity and specificity of colonoscopy for detection of CRC is 100%. Thus, patients with a positive colonoscopy/CTC all have CRC and those with a negative colonoscopy result do not have the target condition	Assumption
10. The symptoms of all those patients with CRC who are FNs will persist such that they will all receive a colonoscopy and thus be diagnosed (within 1 year) should they survive	NG12[6]/expert opinion
11. Patients who had FN gFOBT or FIT, and whose symptoms persisted, have an increased probability of progressing to a worse cancer state due to the delay to diagnosis	
12. Probability of delayed diagnosis of CRC was assumed to be the probability of progression within Dukes' states at 6 months	Assumption
13. TN, FP and FN patients who become asymptomatic do not have the target condition	
14. The model assumes that only those patients with a negative test result, and whose symptoms do not persist, do not receive a colonoscopy/CTC	
15. A CT scan of the chest, abdomen and pelvis is performed for all of the patients testing positive for CRC after colonoscopy or CTC, to estimate the stage (Dukes' A–D) of the disease	NG12[6]
16. For the base-case scenario, we considered a threshold of 10 μg Hb/g faeces or equivalent for the detection of CRC using a single faecal sample. Other options were explored in sensitivity analyses	Assumption
17. The prevalence of CRC in the base-case population was assumed to be 1.5%	NG12[6]
CRC Markov model	
18. After the initial distribution of patients in the CRC model is determined, patients may stay in their current health state, progress to the health state representing the next worsening in the condition or die (from CRC or another cause)	NG12[6]
19. Costs associated with the health states of the CRC Markov model were estimated as lifetime costs (i.e. one-off cost)	
Healthy population Markov model	
20. Patients entering this model can either die of all of the causes or stay in the 'alive' health state	Assumption
21. We assumed for the base-case scenario patients aged ≥ 40 years	NG12[6]
Adverse events	
22. The adverse events included in the diagnostic model are bowel bleeding, perforation and death	Literature
23. Reduction of quality of life due to adverse events is assumed to be negligible within a lifetime	Assumption
24. No costs of patients who die due to adverse events of colonoscopy	
25. Adverse events due to CTC were assumed to be the same as those of colonoscopy	
Test costs	
26. Costs of laboratory staff to analyse the test were assumed to be the same for faecal immunochemical testing and guaiac faecal occult blood testing	Assumption
27. Training costs and the costs of the laboratory staff for analysing the test results were not included in the total costs because it was assumed that these are the same for faecal immunochemical testing and guaiac faecal occult blood testing	
28. Costs of the material needed to analyse a sample include costs of the reagents, buffer, reaction cells and analyser cups	
29. Maintenance costs for HM-JACKarc and OC-Sensor were assumed to be equal	

TABLE 43 Main model assumptions (*continued*)

General	Source
Other costs	
30. Costs of colonoscopy/CTC, adverse event costs and CT costs were included in the diagnostic model	NG12[6]
31. We assumed that the cost of colonoscopy/CTC includes the costs of a follow-up appointment with a gastroenterologist	Assumption/expert opinion
32. For test-negative patients whose symptoms persist, an additional GP appointment cost was considered	Assumption
33. Indirect costs parameters were not included in the model, given the perspective of the NHS	

Model analyses

Expected costs and effects, the latter expressed in LYs and QALYs, were estimated for all of the diagnostic tests considered in this assessment. Costs were estimated from the perspective of the NHS in England and Wales. All costs and effects were discounted by 3.5%. The model's time horizon was set to lifetime. Incremental costs and incremental QALYs for each strategy compared with the next best alternative and compared with the comparators (colonoscopy or guaiac faecal occult blood testing) were calculated. By dividing the incremental costs by the incremental QALYs, the ICER was then calculated. The uncertainty about the model input parameters and the potential impact on the model results were explored by scenario, one-way deterministic analyses and PSAs. A series of one-way sensitivity analyses were conducted, whereby the value of one input parameter was changed and its effect on the overall outcome was recorded and assessed. The impact of statistical uncertainties regarding the model's input parameters was explored through PSA. The results of 5000 iterations were presented in the cost-effectiveness plane for all of the interventions compared. Cost-effectiveness acceptability curves (CEACs) were used to describe the probability of an intervention being considered cost-effective, given a threshold ICER. The different probability distributions used in the PSA were described above (see *Model structure and methodology*).

Scenario analyses

Scenario analyses were performed to explore the impact on costs and QALYs of using different assumptions on diagnostic accuracy of faecal immunochemical testing/guaiac faecal occult blood testing, prevalence, test costs, initial and delayed CRC diagnosis, probability of CRC progression, probability of remaining symptomatic after a negative test result, adverse events (including mortality) attributable to colonoscopy, probability of being referred to colonoscopy (vs. CTC) and probability of receiving a second FIT/gFOBT.

Diagnostic accuracy of faecal immunochemical testing/guaiac faecal occult blood testing

In the base-case scenario, we assumed for faecal immunochemical testing a threshold of 10 µg Hb/g faeces or equivalent for the detection of CRC using a single faecal sample. For guaiac faecal occult blood testing we assumed the accuracy estimates in NG12.[6] In these additional scenarios, we considered other sources for the accuracy estimates for guaiac faecal occult blood testing, other thresholds for faecal immunochemical testing, and the inclusion of FOB Gold as an intervention in the analysis. A summary of the additional scenarios on the accuracy of faecal immunochemical testing/guaiac faecal occult blood testing can be seen in *Table 44*.

Prevalence of colorectal cancer

In the base-case scenario, it was assumed that the prevalence of CRC was 1.5%, as in NG12.[6] We explored the scenarios in which prevalence was assumed to be 3% (also explored in NG12[6]) and 5.4% (the highest value found in our systematic review). We considered an additional scenario with a wide uncertainty range (mean 1.5%, lower limit 1% and upper limit 5.4%) to investigate how this would impact on the PSA results.

TABLE 44 Scenario settings for accuracy of faecal immunochemical testing/guaiac faecal occult blood testing

Scenario	Threshold FIT	FIT accuracy estimates (sensitivity, specificity)[a]	gFOBT accuracy estimates: sensitivity, specificity
Base case	10 µg Hb/g faeces	OC-Sensor (92.1%, 85.8%); HM-JACKarc (100%, 76.6%)	50.0%, 88.0%[1]
Accuracy–I	10 µg Hb/g faeces	OC-Sensor (92.1%, 85.8%); HM-JACKarc (100%, 76.6%)	69.2%, 73.2%[92]
Accuracy–II	10 µg Hb/g faeces	OC-Sensor (92.1%, 85.8%); HM-JACKarc (100%, 76.6%)	75%, 79.4%[93]
Accuracy–III	0 µg Hb/g faeces	OC-Sensor (100%, 43.3%)	50.0%, 88.0%[1]
Accuracy–IV	OC-Sensor ≥ 20 µg Hb/g faeces; (confidential information has been removed)	OC-Sensor (89.5%, 86.6%); (confidential information has been removed)	50.0%, 88.0%[1]
Accuracy-V	OC-Sensor and HM-JACKarc 10 µg Hb/g faeces; (confidential information has been removed)	OC-Sensor (92.1%, 85.8%); HM-JACKarc (100%, 76.6%); (confidential information has been removed)	50.0%, 88.0%[1]

a Accuracy estimates for the OC-Sensor, HM-JACKarc and FOB Gold are reported in *Tables 6*, *11* and *17*, respectively.

Costs of faecal immunochemical testing/guaiac faecal occult blood testing

The cost estimates for faecal immunochemical testing and guaiac faecal occult blood testing that are reported in the literature vary significantly and the assumptions made to derive those estimates are not always presented in a transparent way. Whereas the cost estimates used in this diagnostic assessment are properly reported, we acknowledge that there is uncertainty around the underlying assumptions leading to them. For this reason, we considered additional scenarios on the test costs. In particular, we performed threshold analyses on the cost differences between tests, and between tests and colonoscopy, to estimate how large these cost differences should be so that the conclusions from the base-case scenario still hold.

Initial and delayed diagnosis

In the base-case scenario, the distribution of patients per Dukes' stages was 13%, 37%, 36% and 14%, for stages A–D, respectively.[98] In these additional scenarios, we first considered the distribution of patients reported by Cubiella *et al.*:[55] this was 16%, 25%, 44% and 14%, for stages A–D, respectively. Then, the distribution of patients estimated by the experts who filled in our questionnaire (19%, 35%, 32% and 15%, for stages A–D, respectively) was chosen. Finally, in the base-case scenario we assumed a delayed diagnosis of 6 months for those patients testing negative with faecal immunochemical testing/guaiac faecal occult blood testing who were persistent in their symptoms. This delay implied a distribution of patients per Dukes' stages equal to 9%, 29%, 32% and 30%, for stages A–D, respectively. For a 1-year delay, this was 6%, 20%, 29% and 45%.

Colorectal cancer mortality and progression

In the base-case scenario, the probability of CRC progression was modelled as in NG12,[6] using progression probabilities for undiagnosed patients with CRC, which were obtained from the Tappenden *et al.* study.[99] Mortality was modelled using observational data on mortality by CRC stage from the NCIN at the time when the initial diagnosis took place.[98] Thus, besides the limitation of using progression probabilities for undiagnosed patients in a model in which patients are considered, it is also questionable whether or not these mortality data included patients who might eventually progress, as the data looked at only the initial diagnosis and subsequent mortality. Therefore, it might be reasonable to consider that the effect of progression could be included in the mortality data. Hence, in this scenario, we considered the latter assumption and the CRC progression probabilities were set to zero in the model.

Probability of persisting in symptoms after having a negative test result

In the base-case scenario, this probability was estimated by the experts who filled in our questionnaire. This value was 32.5%. In this scenario we explored the consequences of doubling and halving this value.

Adverse events associated with colonoscopy

In the base-case scenario, we considered a mortality rate associated with colonoscopy of 0.0029%. This was based on the study by Reumkens *et al.*[113] To investigate the impact of this assumption on the cost-effectiveness results, we considered in this scenario the highest value that was found in the literature for the mortality due to colonoscopy; this was 0.0970% and it was reported by Day *et al.*[114] for elderly patients undergoing colonoscopy. Additionally, we explored a scenario for which no adverse events (including mortality) were considered.

Probability of being referred to colonoscopy versus computed tomography colonography

The probability of undergoing colonoscopy as opposed to CTC was estimated to be 83% by four experts. The study by Logan *et al.*[126] found that, for approximately 98% of the screening patients with an abnormal test result, the first investigation was colonoscopy. In this scenario, we assumed that all patients would be referred to colonoscopy. Note that, as it was also assumed that adverse event rates were equal for colonoscopy and CTC, differences between this and the base-case scenario are expected to be observed only on the costs side.

Probability of receiving a second faecal immunochemical test/guaiac faecal occult blood test

In our base-case scenario, we assumed that patients who after testing negative remain symptomatic were referred for a colonoscopy or CTC. However, the clinical experts consulted indicated that approximately 20% of these patients would have a second FIT/gFOBT.

Results of cost-effectiveness analyses

Base-case analysis

The base-case lifetime results, reported as cost per QALY gained (ICER) per patient and strategy, are summarised in *Table 45*. From these results, it is clear that the difference in QALYs between all of the strategies is minimal and that the no triage strategy (referral straight to colonoscopy) is the most expensive one.

Note that, where the question is whether or not to recommend faecal immunochemical testing instead of guaiac faecal occult blood testing, then the pairwise comparisons of the different FIT assays against gFOBT assays may be more informative than the full incremental analysis shown above. The base-case ICERs for

TABLE 45 Lifetime results for all of the strategies in the base-case scenario (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28			
OC-Sensor	18.6239	244.42	0.00198	12.14	6133
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc[a]		
HM-JACKarc	18.6242	274.75	0.0003	30.33	88,798

a 'No triage' is not dominated by the OC-Sensor. There is, in fact, a minor difference in QALYs in favour of no triage, which cannot be observed when the figures are rounded to the fourth decimal place.

the two interventions against guaiac faecal occult blood testing are presented in *Table 46*. In both cases, the ICER was < £30,000. Therefore, both interventions are deemed cost-effective compared with guaiac faecal occult blood testing. *Table 46* also shows the results obtained when the comparator is no triage (referral straight to colonoscopy). The HM-JACKarc strategy dominates no triage (referral straight to colonoscopy); it results in more QALYs and it is cost saving. It should be noted that, the ICER obtained when the OC-Sensor was compared with no triage (referral straight to colonoscopy) is extremely high (£4,133,559) but that this results from both negative incremental costs and incremental QALYs (i.e. the ICER is in the south-west quadrant of the cost-effectiveness plane); in this case, the cost savings outweigh the loss in QALYs and, therefore, the OC-Sensor strategy is more cost-effective than no triage (referral straight to colonoscopy).

Finally, *Table 47* shows the breakdown of the total costs and total QALYs for all of the strategies that were included in the analysis. As some values were very small (e.g. number of adverse events or deaths), the number of patients per outcome of the diagnostic model is multiplied by 1000. Costs and QALYs are shown per patient, for consistency with *Table 45* above. Note that number of patients with the disease might be lower than the prevalent CRC population. This is simply because in the model we assumed three possible outcomes of colonoscopy: positive, negative and death. Therefore, those dead, who eventually had CRC, were not counted as having the disease. The number of positive tests was the largest for HM-JACKarc (245.36), followed by OC-Sensor (153.50) and gFOBT (130.28). In the model, all of these patients were assumed to be referred for further investigation with colonoscopy or CTC. Following further investigation, the number of patients with CRC who had a positive FIT was 14.99 for HM-JACKarc, 13.80 for OC-Sensor and 7.49 for gFOBT. Thus, all patients with CRC tested positive with HM-JACKarc, compared with approximately 92% with OC-Sensor and 50% with gFOBT. The immediate consequence of this was that diagnosis of CRC was delayed in no patients tested with HM-JACKarc, in 8% of patients tested with OC-Sensor and in 50% of patients with with gFOBT. The apparent advantage of FIT with respect to gFOBT in detecting patients with CRC earlier comes at the cost of performing more colonoscopies, as the total number of colonoscopies performed was 490.62 for HM-JACKarc, 428.61 for OC-Sensor and 412.95 for gFOBT. This also implies that total costs and risks associated with colonoscopy are higher for FIT than for gFOBT. Because of this, and because performing a FIT was estimated to have a higher cost than gFOBT, the HM-JACKarc diagnostic strategy was more expensive (£255.27) than the OC-Sensor (£225.16) and gFOBT (£214.17) strategies. All testing strategies were clearly cheaper than no triage (£484.19).

Differences in QALYs between the four strategies were minimal. For HM-JACKarc, OC-Sensor and no triage (referral straight to colonoscopy), the total QALYs gained were 0.9048 per patient for the first year (diagnostic phase). For gFOBT this was 0.9044. In fact, there was a difference in QALYS between HM-JACKarc, OC-Sensor and no triage (referral straight to colonoscopy) observed at the fifth decimal place. QALYs were the highest for HM-JACKarc, followed by no triage (referral straight to colonoscopy) and OC-Sensor. This was because for HM-JACKarc no delayed diagnosis was observed. Thus, the difference in QALYs between HM-JACKarc and no triage (referral straight to colonoscopy) was due only to the number of colonoscopies. This was smaller for HM-JACKarc and, therefore, fewer deaths occurred with this strategy. When compared with OC-Sensor, both no triage (referral straight to colonoscopy) and HM-JACKarc strategies, resulted in more

TABLE 46 Lifetime results for intervention vs. comparator in the base-case scenario (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	42.47	18,296
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.14	6133
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259.25	4,133,559

TABLE 47 Breakdown of lifetime results for all of the strategies in the base-case scenario (deterministic)

	No triage (referral straight to colonoscopy)			gFOBT			OC-Sensor			HM-JACKarc		
	Patients (× 1000)	Costs (£)	QALYs	Patients (× 1000)	Costs	QALYs	Patients (× 1000)	Costs (£)	QALYs	Patients (× 1000)	Costs (£)	QALYs
Branch: test +				130.2889	0.10	0.1160	153.5014	0.70	0.1350	245.3629	1.48	0.2182
Colonoscopy +	14.9996	7.19	0.0086	7.4998	3.59	0.0043	13.8082	6.62	0.0079	14.9996	7.19	0.0086
AE bleeding	0.0390	0.02	–	0.0195	0.01	–	0.0359	0.02	–	0.0390	0.02	–
AE perforation	0.0075	0.02	–	0.0037	0.01	–	0.0069	0.02	–	0.0075	0.02	–
Dukes' A	1.9778	0.23	0.0015	0.9889	0.11	0.0007	1.8207	0.21	0.0013	1.9778	0.23	0.0015
Dukes' B	5.5341	0.64	0.0039	2.7670	0.32	0.0019	5.0945	0.59	0.0036	5.5341	0.64	0.0039
Dukes' C	5.3877	0.62	0.0027	2.6939	0.31	0.0013	4.9598	0.58	0.0025	5.3877	0.62	0.0027
Dukes' D	2.0999	0.24	0.0005	1.0500	0.12	0.0003	1.9331	0.22	0.0005	2.0999	0.24	0.0005
Colonoscopy –	984.9714	472.07	0.8963	122.7853	58.85	0.1117	139.6887	66.95	0.1271	230.3562	110.40	0.2096
AE bleeding	2.5609	1.54	–	0.3192	0.19	–	0.3632	0.22	–	0.5989	0.36	–
AE perforation	0.4925	1.59	–	0.0614	0.20	–	0.0698	0.23	–	0.1152	0.37	–
Death	0.0290	0.01	0.0000	0.0038	0.00	0.0000	0.0045	0.00	0.0000	0.0071	0.00	0.0000
Branch: test –				869.7111	0.67	0.7884	846.4986	3.83	0.7698	754.6371	4.56	0.6867
Symptoms				282.6561	–	–	275.1120	–	–	245.2571	–	–
Colonoscopy +				7.4998	3.92	0.0038	1.1914	0.62	0.0006	0.0000	–	0.0000
AE bleeding				0.0195	0.01	–	0.0031	0.00	–	0.0000	–	–
AE perforation				0.0037	0.01	–	0.0006	0.00	–	0.0000	–	–
Dukes' A				0.7021	0.08	0.0005	0.1115	0.01	0.0001	0.0000	–	0.0000
Dukes' B				2.1407	0.25	0.0015	0.3401	0.04	0.0002	0.0000	–	0.0000
Dukes' C				2.4352	0.28	0.0012	0.3868	0.04	0.0002	0.0000	–	0.0000
Dukes' D				2.2218	0.26	0.0006	0.3529	0.04	0.0001	0.0000	–	0.0000

continued

TABLE 47 Breakdown of lifetime results for all of the strategies in the base-case scenario (deterministic) (*continued*)

	No triage (referral straight to colonoscopy)			gFOBT			OC-Sensor			HM-JACKarc		
	Patients (× 1000)	Costs (£)	QALYs	Patients (× 1000)	Costs	QALYs	Patients (× 1000)	Costs (£)	QALYs	Patients (× 1000)	Costs (£)	QALYs
Colonoscopy –				275.1481	143.98	0.2504	273.9127	143.33	0.2493	245.2499	128.33	0.2232
AE bleeding				0.7154	0.43	–	0.7122	0.43	–	0.6376	0.38	–
AE perforation				0.1376	0.44	–	0.1370	0.44	–	0.1226	0.40	–
Death				0.0082	0.00	0.0000	0.0080	0.00	0.0000	0.0071	0.00	0.0000
No symptoms				587.0550	–	0.5342	571.3866	–	0.5200	509.3800	–	0.4635
Total diagnostic		484.19	0.9048		214.17	0.9044		225.16	0.9048		255.27	0.9048
Total healthy Markov			17.6968			17.6971			17.6971			17.6970
CRC Markov		19.48	0.0222		18.10	0.0203		19.26	0.0219		19.48	0.0222
Total lifetime		503.67	18.6239		232.28	18.6218		244.42	18.6239		274.75	18.6242

AE, adverse event.

colonoscopies being performed, implying more deaths with the last two strategies. However, for OC-Sensor, delayed diagnosis was observed, and this seemed to 'outweigh' the gain in QALYs due to fewer deaths.

Note, finally, that the differences in costs and QALYs observed in the two Markov models between the four strategies were also minimal. The healthy population Markov model was used to account for lifetime QALYs of patients who did not have the target condition. The number of QALYs accrued in this model was simply determined by the initial number of patients entering in the model. This was the highest for guaiac faecal occult blood testing, as this was the strategy leading to the fewest colonoscopies and, therefore, the fewest deaths. Hence, the total number of QALYs estimated by the healthy population Markov model was 17.6971 for gFOBT and OC-Sensor (higher than gFOBT in the fifth decimal place), 17.6970 for HM-JACKarc and 17.6968 for no triage (referral straight to colonoscopy). Likewise, the total costs and QALYs estimated by the CRC Markov model were determined only by the initial distribution of patients per Dukes' stage entering in the model. Note that all of the four strategies correctly diagnosed all CRC alive patients. Thus, although the total number of patients entering the model was approximately the same (prevalence minus those who died) for all of the strategies, differences in staging were observed, due to delayed diagnosis, with the gFOBT and OC-Sensor strategies. Because of this, estimated costs (£19.48) and QALYs (0.0222) were higher for no triage (referral straight to colonoscopy) and HM-JACKarc, as for these two strategies no delayed diagnosis was observed. Compared with gFOBT and OC-Sensor, these patients with CRC were healthier and, therefore, lived longer, but also incurred more costs. For gFOBT, diagnosis of CRC was delayed in 50% of patients, the highest among the four strategies compared. Thus, costs and QALYs estimated by the CRC Markov model for gFOBT were the lowest (£18.10 and 0.0203, respectively). Finally, for OC-Sensor, 8% delayed diagnosis was observed. Therefore, costs (£19.26) and QALYs (0.0219) estimated by the CRC Markov model for this strategy were similar to (but slightly lower than) those estimated for HM-JACKarc and no triage (referral straight to colonoscopy).

Sensitivity analysis

The cost-effectiveness results from the PSA are very similar to the deterministic results except that, in this simulation, the ICERs calculated in the PSA were lower than those shown in *Table 45*. These results are presented in *Table 48*.

The probabilistic ICERs for the two interventions compared with every comparator are shown in *Table 49*. These results are also similar to those presented in *Table 46* for the deterministic case, and so are the conclusions drawn.

The scatterplot of the PSA outcomes in the cost-effectiveness plane in *Figure 15* shows that the uncertainty around QALYs is similar for all of the strategies, but the uncertainty around costs is clearly larger (and with higher cost values) for the no triage (referral straight to colonoscopy) strategy. The CEACs for each strategy are shown in *Figure 16*. It can be observed that at low values of the ICER threshold, the probability of being cost-effective is higher for those strategies with lower costs (i.e. gFOBT and OC-Sensor). As the ICER threshold increases, the CEAC for HM-JACKarc increases, whereas those for gFOBT and OC-Sensor decrease.

TABLE 48 Lifetime results for all of the strategies in the base-case scenario (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6415	230.49	NA	NA	NA
OC-Sensor	18.6439	242.51	0.0024	12.02	5039
No triage (referral straight to colonoscopy)	18.6440	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6444	272.50	0.0005	29.99	61,619

NA, not applicable.

TABLE 49 Lifetime results for intervention vs. comparator in the base-case scenario (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0029	42.01	14,626
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0004	–228.10	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0024	12.02	5039
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–258.09	2,578,543

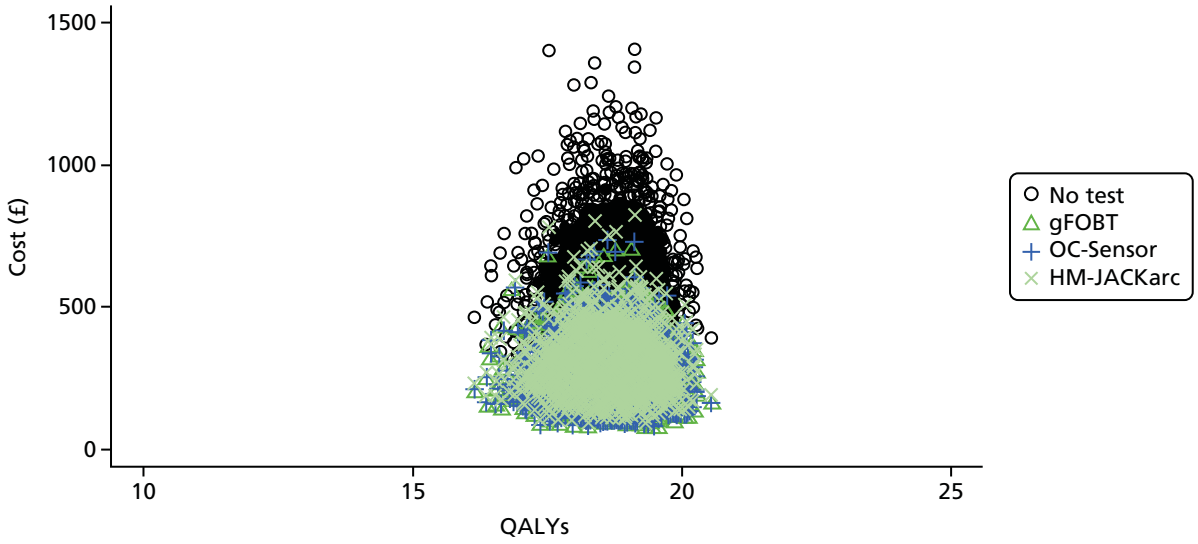

FIGURE 15 Cost-effectiveness plane with PSA outcomes for all of the strategies in the base-case scenario.

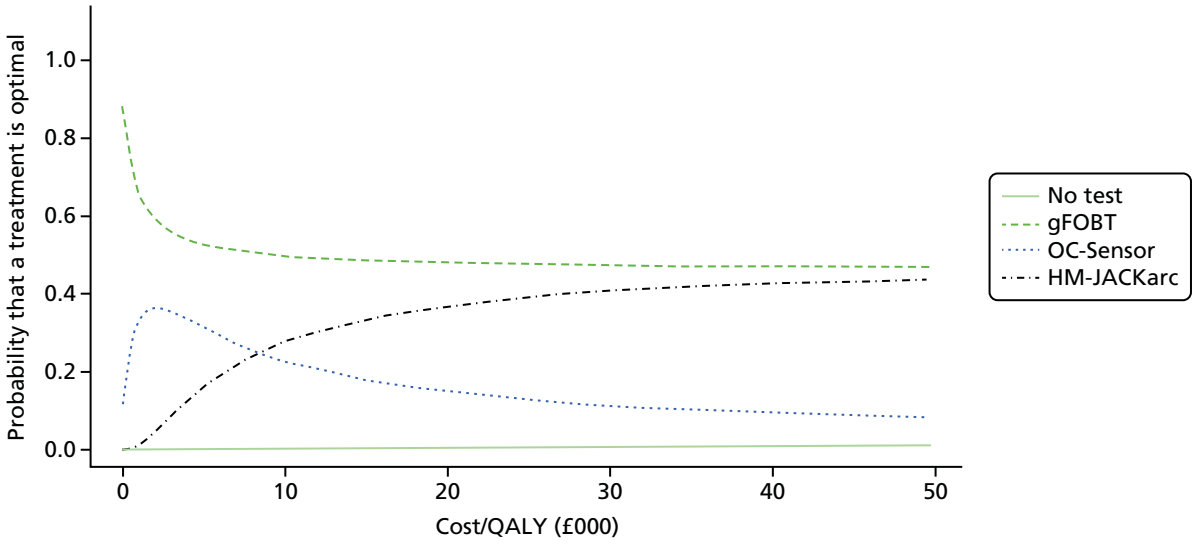

FIGURE 16 Cost-effectiveness acceptability curves for all of the strategies in the base-case scenario.

Both CEACs for HM-JACKarc and gFOBT seem to converge to 0.5, but for all values of the ICER threshold considered in this analysis the cost-effectiveness probability for gFOBT was the highest. In particular, at the ICER threshold equal £30,000, the cost-effectiveness probabilities for gFOBT, HM-JACKarc, OC-Sensor and no triage (referral straight to colonoscopy) were 0.47, 0.41, 0.11 and 0.01, respectively.

Pairwise comparisons of the two different FIT assays against the two comparators included in this diagnostic assessment (gFOBT and no triage) were also explored in the PSA. The results are presented in *Figure 17* (cost-effectiveness planes) and *Figure 18* (CEACs). When the comparator was no triage (referral straight to colonoscopy), all PSA outcomes were located in the southern quadrants of the cost-effectiveness plane, indicating cost savings. They seem to be evenly scattered over the two quadrants. Thus, for approximately half of the PSA outcomes the cost savings due to faecal immunochemical testing do not outweigh the loss in QALYs and, therefore, the FIT strategies are no more cost-effective than no triage (referral straight to colonoscopy). However, as most of the PSA outcomes are located very close to the *y*-axis (where incremental QALYs are zero), no triage (referral straight to colonoscopy) will be cost-effective compared with HM-JACKarc, or OC-Sensor, only for very large values of the ICER threshold. In fact, this was not observed for any of the values of the ICER threshold that were considered in the CEACs shown in *Figure 18*. When the comparator was gFOBT, the PSA outcomes were mostly located in the northern quadrants of the cost-effectiveness plane (given that faecal immunochemical testing is more expensive). When the intervention was the OC-Sensor, we observed PSA outcomes scattered over the four quadrants of the cost-effectiveness plane, indicating that there is large uncertainty about which strategy is the most cost-effective. Note, finally, that the probabilistic ICERs for both HM-JACKarc compared with gFOBT (£14,626) and OC-Sensor compared with gFOBT (£5039) were estimated to be in the north-east quadrant of the cost-effectiveness plane, with an ICER of < £30,000, meaning that on average the FIT strategies are cost-effective compared with gFOBT. However, this is not readily apparent when we

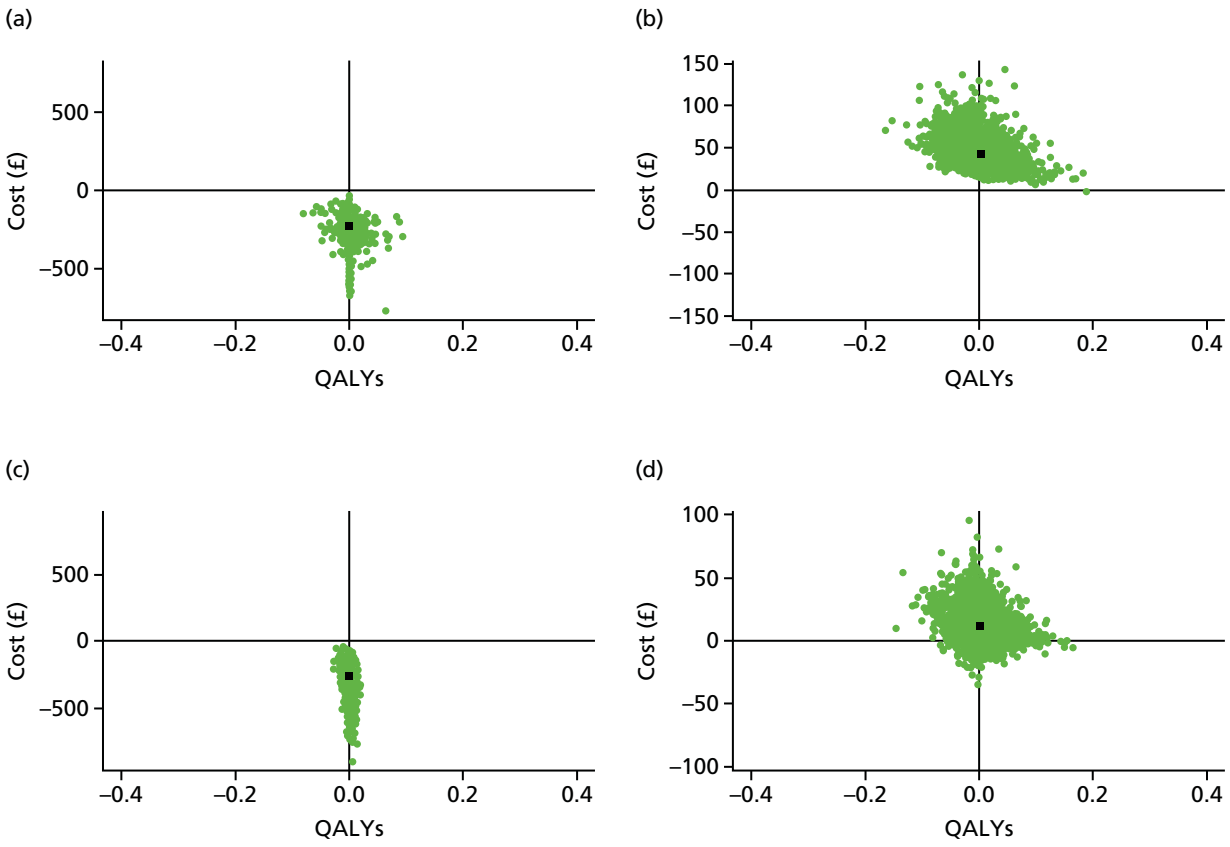

FIGURE 17 Cost-effectiveness plane with PSA outcomes for intervention vs. comparator in the base-case scenario. (a) Cost-effectiveness plane – HM-JACKarc vs. no test; (b) cost-effectiveness plane – HM-JACKarc vs. gFOBT; (c) cost-effectiveness plane – OC-Sensor vs. no test; and (d) cost-effectiveness plane – OC-Sensor vs. gFOBT.

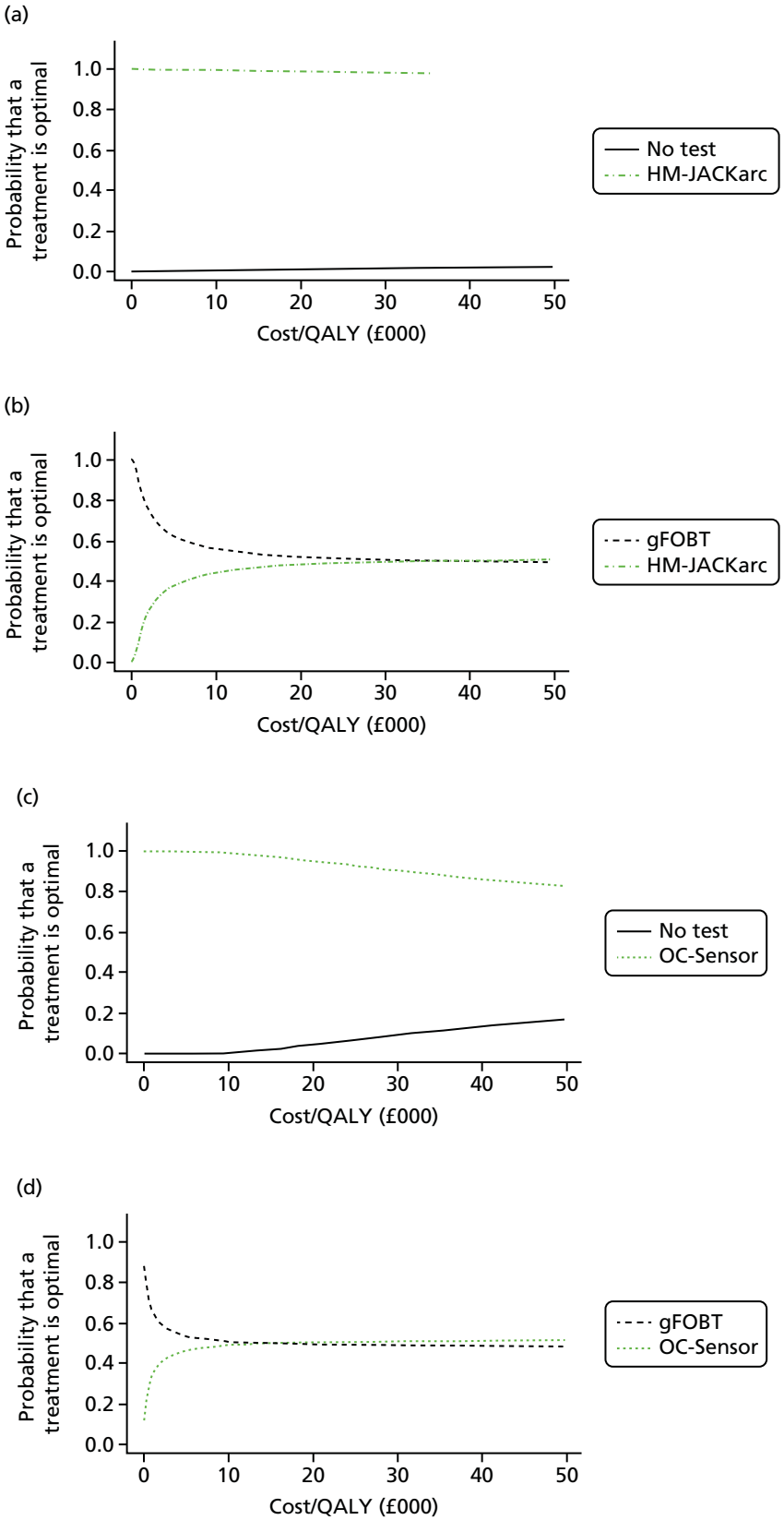

FIGURE 18 Cost-effectiveness acceptability curves for intervention vs. comparator in the base-case scenario. (a) Acceptability curves (HM-JACKarc vs. no test); (b) acceptability curves (HM-JACKarc vs. gFOBT); (c) acceptability curves (OC-Sensor vs. no test); and (d) acceptability curves (OC-Sensor vs. gFOBT).

observed the CEACs in *Figure 18*, as these cross each other at values of the ICER threshold that are much larger than the probabilistic ICERs. This can be explained by the asymmetry of the distribution of the PSA outcomes on the cost-effectiveness plane. Nevertheless, given the small difference in QALYs between all of the strategies observed in the results, the conclusions from the PSA regarding which strategy is the most cost-effective are expected to be sensitive to changes in the accuracy estimates. This is explored in several scenarios within the next section.

Scenario analysis

In the scenarios presented below, only the most significant differences with respect to the base-case scenario are discussed. Complete results are provided in *Appendix 11*.

Diagnostic accuracy of faecal immunochemical test/guaiac faecal occult blood test

Accuracy scenario I: guaiac faecal occult blood test accuracy estimates based on the Niv and Sperber study

In this scenario analysis, we considered the accuracy estimates for guaiac faecal occult blood testing reported by Niv and Sperber,[92] as these are considered more representative of the population of this diagnostic assessment than those reported in NG12.[6] The only difference with respect to the base-case results can be observed in the gFOBT estimates. In this case, the total QALYs and total costs estimated per patient were 18.6227 and £277.54, respectively. Thus, in this scenario, guaiac faecal occult blood testing was dominated by both FIT strategies. Probabilistic results show that the main difference with respect to the base-case scenario was that guaiac faecal occult blood testing was now clearly less cost-effective. This can be seen in the CEACs plot for all of the strategies in *Figure 19*, where guaiac faecal occult blood testing is the most cost-effective strategy only when the ICER threshold ranges between (approximately) £12,750 and £24,500 (whereas in the base-case gFOBT was the most cost-effective strategy for the whole range of ceiling ratios that were considered in the analysis). The CEACs for each intervention compared with guaiac faecal occult blood testing separately are presented in *Figure 20*. These show that both interventions are more cost-effective than guaiac faecal occult blood testing for all of the ceiling ratio values that were considered in this analysis.

Accuracy scenario II: guaiac faecal occult blood test accuracy estimates based on the Bjerregaard et al. *study*

The accuracy estimates for guaiac faecal occult blood testing reported in Bjerregaard *et al.*[93] were considered for this scenario, as these are also regarded as more representative of the population of this diagnostic assessment than those in NG12.[6] In this scenario, the total QALYs and total costs estimated

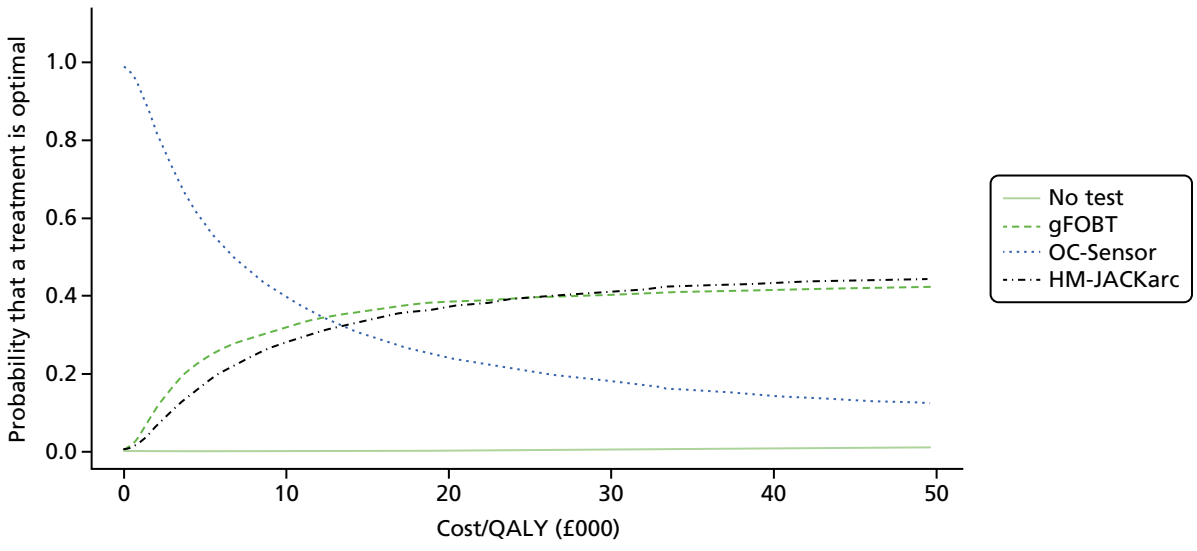

FIGURE 19 Cost-effectiveness acceptability curves for all of the strategies: alternative gFOBT accuracy estimates.

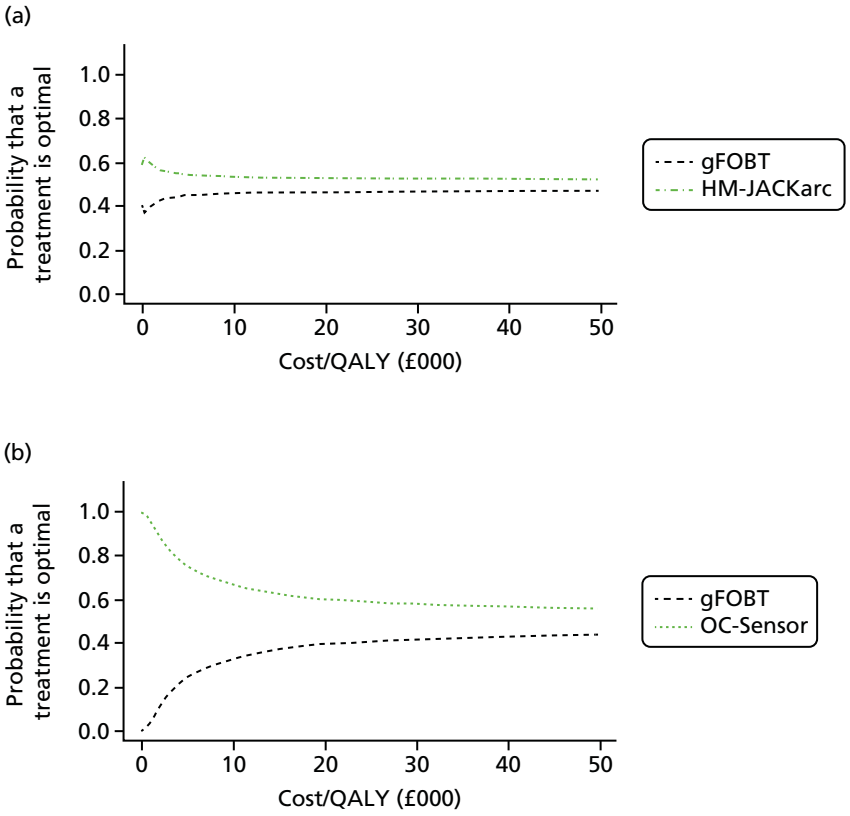

FIGURE 20 Cost-effectiveness acceptability curves for intervention vs. gFOBT, alternative gFOBT accuracy estimates. (a) acceptability curves – HM-JACKarc vs. gFOBT; and (b) acceptability curves – OC-Sensor vs. gFOBT.

per gFOBT patient were 18.6230 and £258.97, respectively. Thus, guaiac faecal occult blood testing was dominated by the OC-Sensor. The ICER reported when the intervention was HM-JACKarc was £13,482. Therefore, at the common value of the ceiling ratio of £30,000, HM-JACKarc was deemed cost-effective compared with guaiac faecal occult blood testing. All of the CEACs were similar to those in the scenario for which the gFOBT accuracy estimates were obtained from Niv and Sperber[92] and, therefore, they are not shown here. The main difference with respect to the previous scenario is that guaiac faecal occult blood testing is now the most cost-effective strategy when the ICER threshold ranges between (approximately) £12,250 and £23,500. The CEACs for each intervention compared with guaiac faecal occult blood testing are also similar, but the cost-effectiveness probability for guaiac faecal occult blood testing is now higher.

Accuracy scenario III: faecal immunochemical test threshold any detectable haemoglobin (OC-Sensor only)

In this scenario, a threshold of any detectable Hb was assumed for faecal immunochemical testing. The idea of this scenario is to look at the effects of using a threshold at the lowest level that faecal immunochemical testing is able to detect. For this threshold, our systematic review obtained data only for the OC-Sensor. The total QALYs and total costs estimated per patient for the OC-Sensor strategy were 18.6240 and £375.40, respectively. For gFOBT and no triage (referral straight to colonoscopy) these were as in the base-case scenario. In this case, no triage (referral straight to colonoscopy) was dominated by the OC-Sensor, and the ICER obtained when the OC-Sensor was compared with gFOBT was £65,192. Thus, at the common value of the ceiling ratio of £30,000, the OC-Sensor was not cost-effective compared with gFOBT. This is illustrated in the CEAC presented in *Figure 21*.

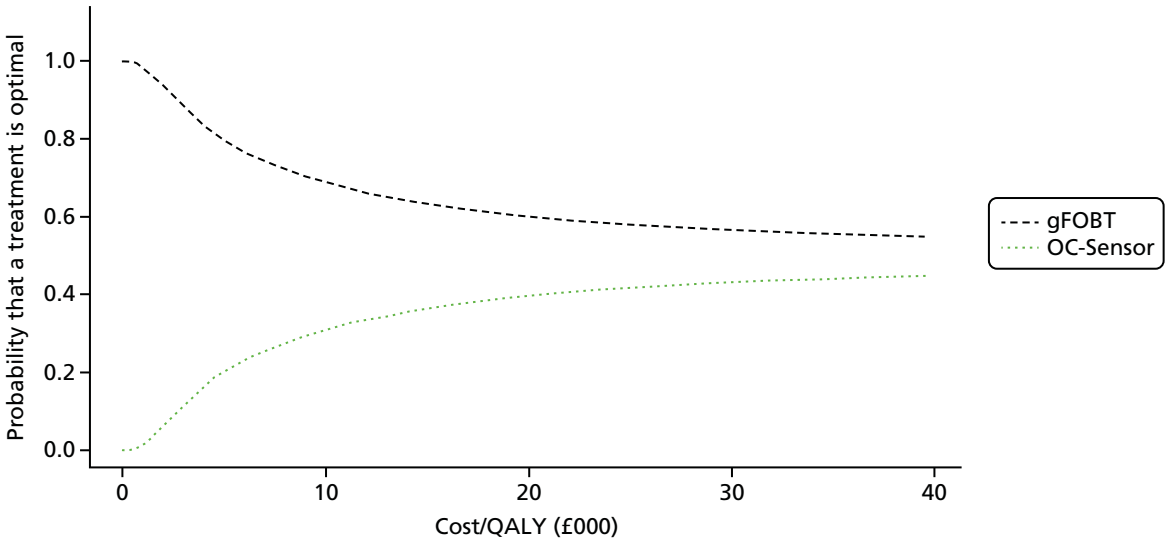

FIGURE 21 Cost-effectiveness acceptability curves for OC-Sensor vs. gFOBT: scenario – any detectable Hb.

Accuracy scenario IV: faecal immunochemical test threshold of ≥ 20 µg Hb/g faeces (OC-Sensor and FOB Gold)

In this scenario, we assumed a threshold of ≥ 20 µg Hb/g faeces. For this threshold, our systematic review obtained data for the OC-Sensor assay and also for the FOB Gold assay. Although the reliability of the accuracy data for the latter was questionable, as explained in detail in *Chapter 3* (see *Diagnostic performance of the FOB Gold faecal immunochemical test assay*), we decided to include this FIT assay in this scenario. Deterministic results are shown in *Table 50*. The no triage (referral straight to colonoscopy) strategy was the most expensive, but also the strategy with the most QALYs. However, as in previous scenarios, little difference in QALYs was observed between any of the strategies.

The ICERs for the two interventions in comparison with guaiac faecal occult blood testing are shown in *Table 51*. In both cases, the ICER was very low (around £5000). Therefore, the two interventions are cost-effective compared with gFOBT. *Table 51* also shows the results obtained when the comparator is no

TABLE 50 Lifetime results for all of the strategies in the scenario of FIT threshold of ≥ 20 µg Hb/g faeces (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28			
FOB Gold	18.6237	240.62	0.0018	8343	4725
OC-Sensor	18.6238	241.83	0.0001	1210	12,576
No triage (referral straight to colonoscopy)	18.6239	503.67	0.0002	261,839	1,449,585

TABLE 51 Lifetime results for intervention vs. comparator: FIT threshold of ≥ 20 µg Hb/g faeces (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
FOB Gold vs. gFOBT	0.0018	8.34	4725
FOB Gold vs. no triage (referral straight to colonoscopy)	–0.0003	–263.05	950,102
OC-Sensor vs. gFOBT	0.0019	9.55	5131
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–261.84	1,449,585

triage (referral straight to colonoscopy). In both cases, the ICERs obtained were very high, but these result from both negative incremental costs and incremental QALYs. In this case, the cost savings outweigh the loss in QALYs and thus the FIT strategies are more cost-effective than no triage (referral straight to colonoscopy).

The CEACs of all of the strategies presented in *Figure 22* show that guaiac faecal occult blood testing is the strategy with the highest probability of being cost-effective for all of the values of the ceiling ratio considered in this analysis. In particular, at an ICER threshold equal to 30,000, this probability was approximately 0.5. The probability of being cost-effective was similar for both interventions, but slightly higher for the FOB Gold. Compared with no triage (referral straight to colonoscopy), both interventions have a higher probability of being cost-effective for all of the values of the ICER threshold considered in the analysis (CEACs not shown). CEACs for each intervention compared with gFOBT are shown in *Figure 23*. We can observe that, at lower values of the ICER threshold, the gFOBT has a higher probability of being cost-effective because the interventions are more expensive. However, as the ICER threshold increases, the probability of the two interventions being cost-effective also increases and becomes slightly higher than that for gFOBT, although in both cases the probability is close to 0.5.

Accuracy scenario V: threshold of ≥ 10 µg Hb/g faeces (base case) including FOB Gold

In this scenario, we included the FOB Gold assay as well as the interventions and comparators that were considered in the base case. We assumed a threshold of 6.8 µg Hb/g faeces for the FOB Gold test, as this was the closest available value to the base-case threshold of ≥ 10 µg Hb/g faeces, and because for this threshold the FOB Gold test showed performance characteristics (sensitivity and specificity) similar to those for the other FITs at the base-case threshold. In the full incremental deterministic analysis, the FOB Gold assay was dominated by the OC-Sensor, and, as no triage (referral straight to colonoscopy) was dominated by HM-JACKarc, the results of this scenario reduce to those in the base case presented in *Table 45*. The ICER of FOB Gold compared with gFOBT was £15,720, and compared with no triage (referral straight to colonoscopy) was £2,273,829 (in the south-west quadrant of the cost-effectiveness plane). Thus, in both cases, FOB Gold is cost-effective given the common threshold ICER of £30,000. The CEACs for each strategy are shown in *Figure 24*. It can be observed that the FOB Gold strategy has a low probability of being cost-effective. This is not surprising, as the full incremental analysis results showed that FOB Gold was dominated by the OC-Sensor. The rest of the CEACs are similar to those obtained in the base-case scenario (see *Figure 16*).

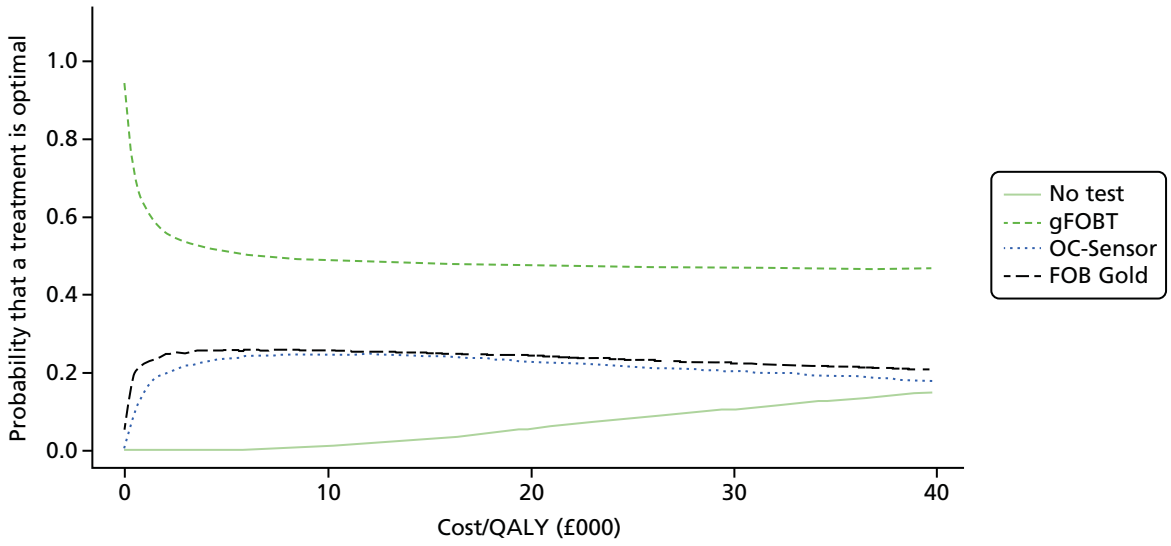

FIGURE 22 Cost-effectiveness acceptability curves for all of the strategies: FIT threshold of ≥ 20 µg Hb/g faeces.

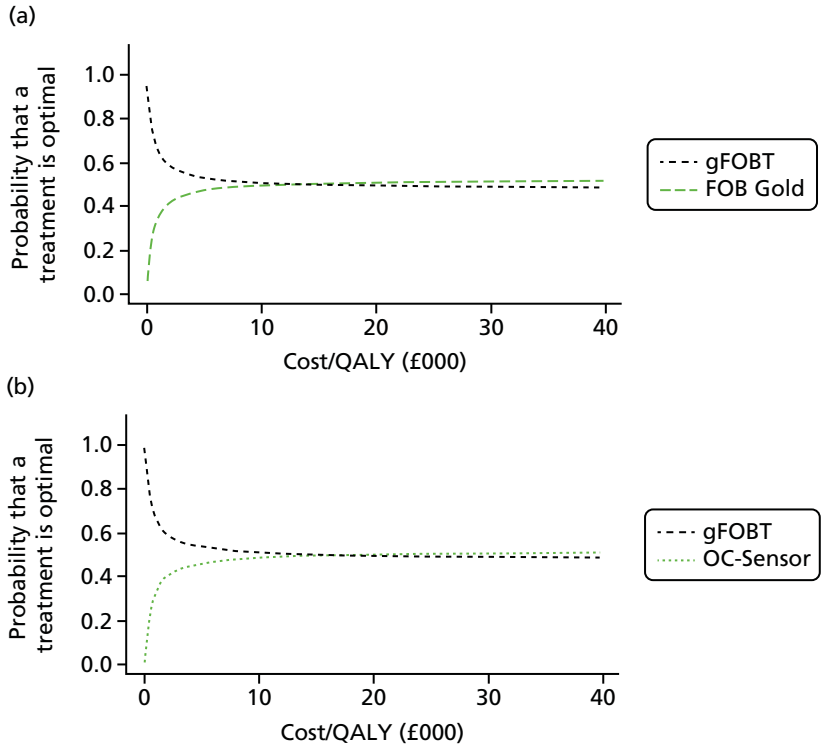

FIGURE 23 Cost-effectiveness acceptability curves for intervention vs. gFOBT: FIT threshold of ≥ 20 µg Hb/g faeces. (a) Acceptability curves – FOB Gold vs. gFOBT; and (b) acceptability curves – OC-Sensor vs. gFOBT.

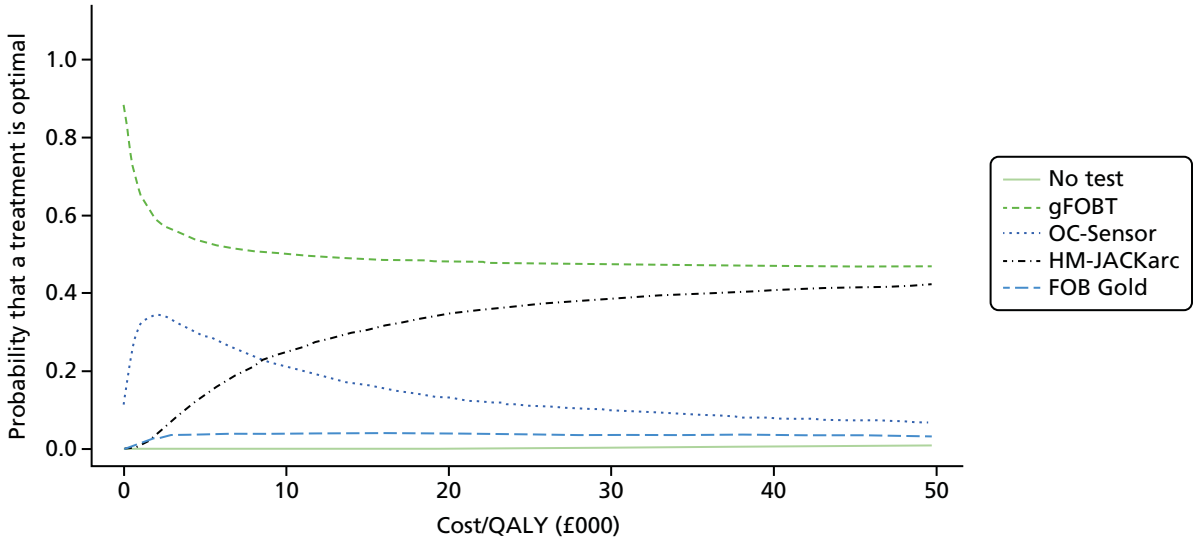

FIGURE 24 Cost-effectiveness acceptability curves for all of the strategies in the scenario including FOB Gold.

The CEACs in *Figure 25* show that the probability of FOB Gold being cost-effective compared with no triage (referral straight to colonoscopy) is high even at large values of the ceiling ratio of the ICER threshold. However, gFOBT clearly more cost-effective than FOB Gold at lower values of the ICER threshold. As the ceiling ratio increases, the probability of being cost-effective for both strategies seems to converge to 0.5.

Prevalence of colorectal cancer

The results of the scenarios with prevalence 3% and 5.4% were similar to those in the base case (*Tables 52* and *53*). In particular, the ICERs obtained in the scenarios in which the two interventions are compared with

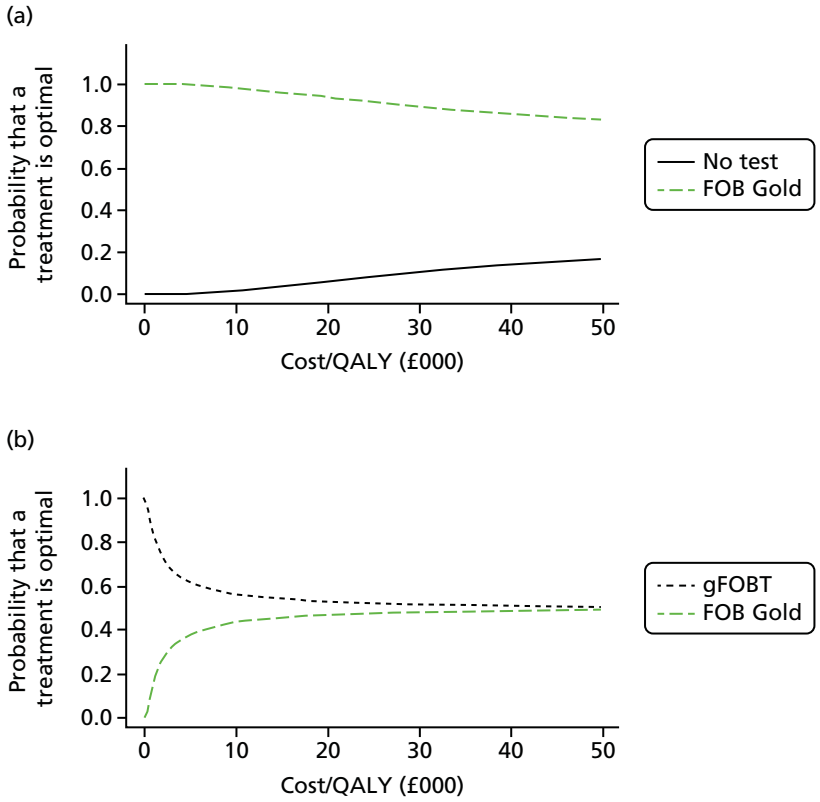

FIGURE 25 Cost-effectiveness acceptability curves for FOB Gold vs. comparator in the scenario including FOB Gold. (a) Acceptability curves – FOB Gold vs. no test; and (b) acceptability curves – FOB Gold vs. gFOBT.

TABLE 52 Lifetime results for intervention vs. comparator, prevalence 3% (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0047	45.68	9754
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–225.34	–820,612
OC-Sensor vs. gFOBT	0.0040	15.19	3829
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–255.83	578,092

TABLE 53 Lifetime results for intervention vs. comparator, prevalence 5.4% (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0085	50.80	6004
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–219.62	–820,054
OC-Sensor vs. gFOBT	0.0071	20.06	2808
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0011	–250.36	238,380

gFOBT are lower than those ICERs obtained in the base-case scenario (< £10,000). Thus, in both cases, the two interventions are deemed cost-effective.

The scenario with an asymmetrical CI changed only the probabilistic results. For this scenario, we assumed a triangular distribution with the most likely value of 1.5% and limits of 1% and 5.4%. Note that, for this choice of parameters, the mean of the triangular distribution is 2.6%. The main consequence of this choice was that the PSA outcomes were more scattered over the cost-effectiveness plane (especially on the QALYs axis), but all CEACs were very similar to those obtained in the base-case scenario (results not shown).

Costs of faecal immunochemical test/guaiac faecal occult blood test (threshold analysis)

For this analysis, we first considered a hypothetical situation in which all test costs were £0. Then we calculated what the cost difference between HM-JACKarc and gFOBT, and between the OC-Sensor and gFOBT, should be in order to obtain an ICER of (approximately) £30,000. From this analysis, we concluded that HM-JACKarc could be up to £32 more expensive than gFOBT while still keeping the ICER < £30,000. OC-Sensor could be up to £51 more expensive than gFOBT. Compared with the no triage (referral straight to colonoscopy) strategy, both FIT strategies were already so much cheaper in the base case that the cost of the tests themselves could be increased by well over £200 and still be cost-effective. Thus, no threshold analysis was needed for this comparator.

Initial and delayed diagnosis

Changing the probability of being in a certain Dukes' stage influenced only the outcomes calculated from the Markov models, as these probabilities are not input parameters for the diagnostic (decision tree) model. Note that, in the base-case scenario, the percentages of patients in each Dukes' stage were 13%, 37%, 36% and 14% for stages A–D, respectively.[98] In these additional scenarios, we first considered the distribution of patients reported in a study included in our systematic review (Cubiella *et al.*[55]); this was 16%, 25%, 44% and 14% for stages A–D, respectively, that is, more patients in stages A and C, but fewer in stage B. The results in *Table 54* are similar to those in the base case, with a slight loss in QALYs for all of the strategies and also lower costs. Both interventions dominated no triage (referral straight to colonoscopy) and, when compared with gFOBT, both ICERs were < £30,000. The PSA results (not shown here) did not show any significant difference with respect to those in the base case.

The distribution of patients (estimated by the experts) who filled in our questionnaire was 19%, 35%, 32% and 15%, for stages A–D, respectively. Thus, there would be more patients in stages A and D, but fewer in stages B and C. The results were also similar to those in the base case, but now with a slight gain in QALYs and an increase in costs for all of the strategies (*Table 55*). In this case, only HM-JACKarc dominated no triage (referral straight to colonoscopy). The ICER for OC-Sensor compared with no triage (referral straight to colonoscopy) was high, but in the south-west quadrant of the cost-effectiveness plane. Therefore, OC-Sensor was cost-effective. When compared with gFOBT both ICERs were < £30,000. The PSA results did not show any significant difference with respect to those in the base case either.

TABLE 54 Lifetime results for intervention vs. comparator, initial distribution from a study in our systematic review (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0019	42.22	22,319
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	–820,947
OC-Sensor vs. gFOBT	0.0016	11.93	7370
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0000	–259.21	–46,570,596

TABLE 55 Lifetime results for intervention vs. comparator, initial distribution by clinical experts (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0032	42.90	13,574
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	–820,947
OC-Sensor vs. gFOBT	0.0027	12.50	4655
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–259.32	1,322,872

Finally, note that in the base-case scenario we assumed a delayed diagnosis of 6 months for those patients who were testing negative with faecal immunochemical testing/gFOBT and were persistent in their symptoms. The 6-month delay implied a distribution of patients, per Dukes stage, equal to 9%, 29%, 32% and 30%, for stages A–D, respectively; for a 1-year delay, this was 6%, 20%, 29% and 45%, respectively, that is, most patients were in stage D. The results shown in *Table 56* are similar to those in the base case, with a slight loss in QALYs for gFOBT and OC-Sensor, and also lower costs. Note that, in the base-case scenario, HM-JACKarc detected all patients with CRC. Therefore, the assumption on the delay of diagnosis had no impact on these results.

Colorectal cancer mortality and progression

The impact of not considering CRC progression explicitly in the model was explored in this scenario. The full incremental results in *Table 57* were similar to those in the base case, with a slight gain in QALYs for all of the strategies and an increase in costs.

When the interventions were compared with gFOBT and no triage (referral straight to colonoscopy) separately (*Table 58*), we observed, as in previous scenarios, that HM-JACKarc dominated no triage (referral straight to colonoscopy); the ICER for OC-Sensor compared with no triage (referral straight to colonoscopy) was large but in the south-west quadrant of the cost-effectiveness plane (hence, OC-Sensor was cost-effective); and the ICERs obtained when the comparator was gFOBT were both < £30,000 (and, therefore, both were cost-effective).

TABLE 56 Lifetime results for intervention vs. comparator, 1-year delayed diagnosis (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0047	43.85	9360
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	–820,947
OC-Sensor vs. gFOBT	0.0040	13.30	3352
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–259.47	592,092

TABLE 57 Lifetime results for all of the strategies: scenario – without CRC progression (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.701	263.92	NA	NA	NA
OC-Sensor	18.711	279.10	0.0101	15.18	1508
No triage (referral straight to colonoscopy)	18.713	538.93	Dominated by HM-JACKarc		
HM-JACKarc	18.713	310.01	0.0019	30.90	16,528

NA, not applicable.

TABLE 58 Lifetime results for intervention vs. comparator: scenario – without CRC progression (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0119	46.09	3859
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	–820,947
OC-Sensor vs. gFOBT	0.0101	15.18	1508
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0016	–259.83	163,305

The main difference with respect to the base-case PSA is that results are now more favourable to the interventions, as can be observed in the CEACs for all of the strategies in *Figure 26* and the CEACs for the interventions against gFOBT in *Figure 27*.

Probability of persisting in symptoms after having a negative test result

In the base-case scenario, this probability was estimated by the experts who filled in our questionnaire. This value was 32.5%. In this scenario we explored the consequences of doubling and halving this value. Doubling the probability of persisting in symptoms after having a negative result had a minor impact on the estimated QALYs, as can be seen in *Table 59*. This resulted in a slight loss in QALYs for all of the testing strategies owing to an increase in the number of patients with a delayed diagnosis. The impact on costs was large, as this implies a larger number of colonoscopies for all of the testing strategies. The ICERs for the interventions compared with gFOBT were low (both < £10,000). In addition, as in previous scenarios, no triage (referral straight to colonoscopy) was dominated by HM-JACKarc and the ICER of OC-Sensor compared with no triage was high, and it lay in the south-west quadrant of the cost-effectiveness plane. The PSA results (not shown) were similar to those in the base case, but in this scenario the interventions were more likely to be deemed cost-effective.

When the probability of persistent symptoms after having a negative result was halved (*Table 60*), the opposite was observed. Nevertheless, in this case, no triage (referral straight to colonoscopy) was dominated by both interventions and the ICERs for both HM-JACKarc and OC-Sensor compared with gFOBT were < £30,000.

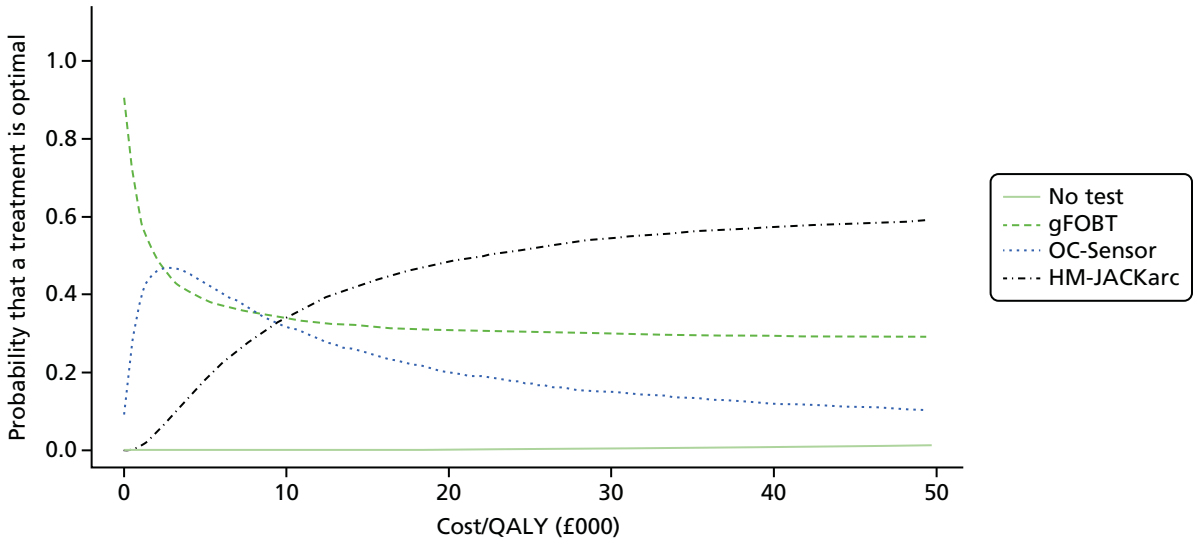

FIGURE 26 Cost-effectiveness acceptability curves for all of the strategies: scenario – without CRC progression.

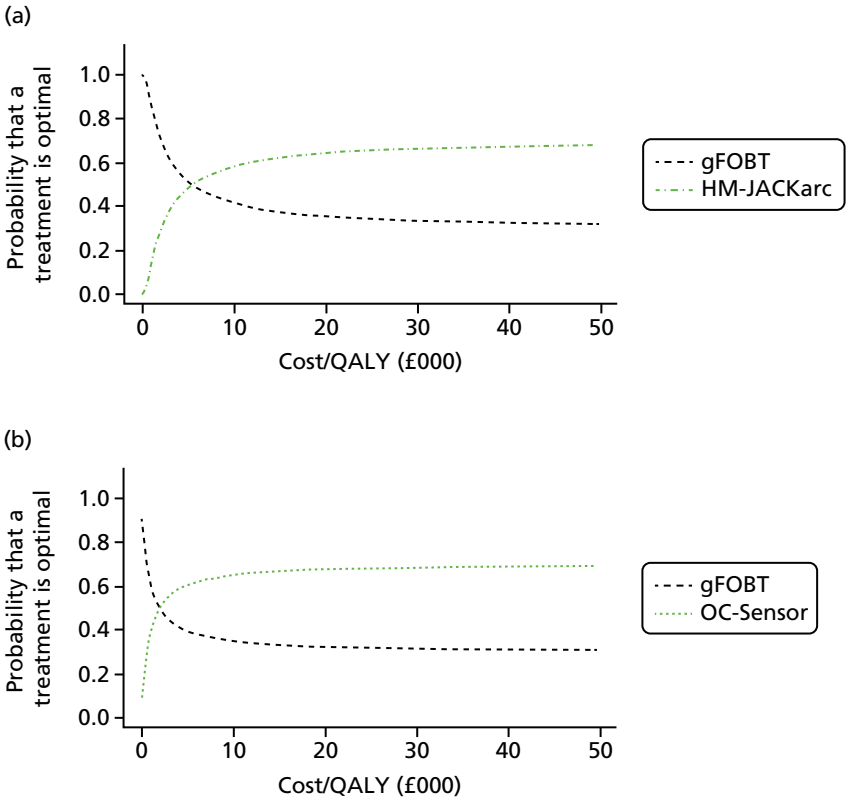

FIGURE 27 Cost-effectiveness acceptability curves for intervention against gFOBT in the scenario without CRC progression. (a) Acceptability curves – HM-JACKarc vs. gFOBT; and (b) acceptability curves – OC-Sensor vs. gFOBT.

TABLE 59 Lifetime results for all of the strategies: scenario – double probability of persisting in symptoms after negative test result (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6217	381.09			
OC-Sensor	18.6237	389.26	0.0020	8.17	4118
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6241	403.87	0.0004	14.61	36,534

TABLE 60 Lifetime results for all of the strategies: scenario – half probability of persisting in symptoms after negative test result (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6220	157.88			
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by OC-Sensor		
OC-Sensor	18.6239	172.01	0.0020	14.13	7143
HM-JACKarc	18.6243	210.19	0.0003	38.19	114,546

Adverse events associated with colonoscopy

We first considered the highest value found in the literature for the mortality due to colonoscopy. This was 0.0970%, and it was reported by Day *et al.*[114] for elderly patients. This can be seen as a worst-case scenario regarding mortality due to colonoscopy. As expected, the main differences with respect to the base-case scenario were observed for those strategies for which the number of colonoscopies was larger: no triage (referral straight to colonoscopy) and HM-JACKarc. The results are shown in *Table 61*; in particular, no triage (referral straight to colonoscopy) was dominated by all of the strategies. Whereas the ICER for OC-Sensor compared with gFOBT was < £10,000, the ICER for HM-JACKarc compared with gFOBT was £45,271. Thus, at the common value for the ICER threshold of £30,000, HM-JACKarc was not cost-effective compared with gFOBT.

When no adverse events were considered (*Table 62*), no triage (referral straight to colonoscopy) was dominated by HM-JACKarc. This was expected because the difference in QALYs between these two strategies observed in the base-case scenario was due to only the adverse events. In this case, as no adverse events were considered, the QALYs estimated were exactly the same. Likewise, differences in QALYs between faecal immunochemical testing and gFOBT are not present in this scenario. Therefore, the results of this scenario are slightly more favourable to faecal immunochemical testing than those in the base-case scenario.

Probability of being referred to colonoscopy versus computed tomography colonography

In this scenario, we assumed that all patients would be referred to colonoscopy. The results are presented in *Table 63*.

As expected, differences between this and the base-case scenario were minor and due to the increase in the costs of colonoscopy. For this reason, the results were slightly better for gFOBT, as this was the strategy that required fewer colonoscopies.

Probability of receiving a second faecal immunochemical test/guaiac faecal occult blood test

In this scenario, we assumed that (on average) 20% of the patients who remain symptomatic after testing negative on FIT/gFOBT had a second FIT/gFOBT. The results are shown in *Table 64*.

TABLE 61 Lifetime results for all of the strategies: scenario – high mortality associated to colonoscopy (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
No triage (referral straight to colonoscopy)	18.6064	503.65	Dominated by gFOBT		
gFOBT	18.6148	232.26			
HM-JACKarc	18.6157	274.73	Dominated by OC-Sensor		
OC-Sensor	18.6165	244.40	0.0017	12.14	7144

TABLE 62 Lifetime results for all of the strategies: scenario – no adverse events associated to colonoscopy (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6221	230.97			
OC-Sensor	18.6241	243.06	0.0020	12.09	6081
No triage (referral straight to colonoscopy)	18.6245	500.49	Dominated by HM-JACKarc		
HM-JACKarc	18.6245	273.19	0.0004	30.13	80,244

TABLE 63 Lifetime results for all of the strategies: scenario – all patients referred to colonoscopy, as opposed to CTC (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	243.73			
OC-Sensor	18.6239	256.31	0.0020	12.58	6352
No triage (referral straight to colonoscopy)	18.6239	531.40	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	288.36	0.0003	32.05	93,832

TABLE 64 Lifetime results for all of the strategies: scenario – FIT-/gFOBT-negative patients who persist in symptoms get a second test (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.32			
OC-Sensor	18.6239	244.67	0.0020	12.35	6237
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	275.05	0.0003	30.38	88,936

As expected, having a second FIT/gFOBT increased the costs of the patients who tested negative on FIT/gFOBT and remained symptomatic. This increase in costs had little impact on the cost-effectiveness results, as, on average, 32.5% of the patients testing negative would persist in their symptoms and 20% of these patients would get the second test. Thus, this increase would have an effect on only 6.5% of the patients who tested negative on FIT/gFOBT.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness

All of the studies included in the systematic review were diagnostic cohort studies reporting accuracy data. Eight published studies[13,52,53,55–58,75] and one unpublished study (Hospital Clinic de Barcelona 2015; Philippa Pinn, personal communication) assessed accuracy of a quantitative FIT method for the target condition of CRC or for the composite target condition of advanced neoplasia (CRC or HRA); the remaining study,[54] which was published as a conference abstract, reported accuracy data for only the composite target condition 'significant bowel disease' (defined as CRC polyps or bleeding). Five studies[13,52,53,55,58] reported accuracy data for the OC-Sensor assay. Three studies[56,57,75] reported accuracy data for the HM-JACKarc automated system. One study,[54] published as an abstract, and one unpublished study (Hospital Clinic de Barcelona 2015) reported accuracy data for the FOB Gold assay. No studies using the RIDASCREEN Hb or the RIDASCREEN Hb/Hp complex assays met the inclusion criteria for this assessment. Two studies of OC-Sensor[53,55] also developed risk scores for CRC or advanced neoplasia that included faecal immunochemical testing; in the case of the COLONPREDICT study,[55] risk score development was reported in a separate publication,[73] namely a manuscript, which was provided ahead of publication (Callum Fraser, personal communication). None of the included studies reported data comparing different FIT assays, or comparing one or more FIT assays with a gFOBT method. No RCTs or CCTs were identified, and no studies provided data on patient-relevant outcomes following faecal immunochemical testing compared with gFOBT or no faecal occult blood testing.

No study reported data that were specific to the population defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms who are at low risk for CRC according to the criteria defined in NG12[1]). Only one study[52] was conducted in a primary care setting, and this study reported that faecal immunochemical testing was ordered by GPs at the point of referral to secondary care. In addition, all of the studies included some participants who had symptoms that may be considered to be associated with a higher probability of CRC and that are components of the criteria for 2-week referral as defined in NG12[1] (e.g. rectal bleeding).

When faecal immunochemical testing was based on a single faecal sample and a threshold of 10 µg Hb/g faeces was applied, sensitivity estimates indicated that a negative test using either OC-Sensor and HM-JACKarc may be considered adequate to rule out CRC; the summary estimate of sensitivity for C-Sensor was 92.1% (95% CI 86.9% to 95.3%), based on four studies, and the only study of HM-JACKarc to assess the 10 µg Hb/g faeces cut-off point reported a sensitivity of 100% (95% CI 71.5% to 100%).[56] The corresponding specificity estimates were 85.8% (95% CI 78.3% to 91.0%) and 76.6% (95% CI 72.6% to 80.3%), respectively. (Confidential information has been removed.) When a hypothetical cohort of 1000 patients is considered, assuming prevalence estimates derived from the included studies, the estimated number of CRC cases that would be missed using each of the three FIT assays (OC-Sensor and HM-JACKarc 10 µg Hb/g faeces threshold and (confidential information has been removed) is 2, 0 and (confidential information has been removed), respectively; under the same assumptions, the number of 'unnecessary' colonoscopies carried out on people without CRC would be 198, 229 and (confidential information has been removed), respectively (see *Chapter 3*, *Results of the assessment of clinical effectiveness assessment*, see *Figures 5a, 9* and *11*). Reducing the threshold to 'any detectable Hb' produced summary estimates of sensitivity and specificity, for OC-Sensor, of 100% (95% CI 87.7% to 100%) and 43.4% (95% CI 39.7% to 47.1%), based on two studies. For the hypothetical cohort of 1000 patients, this lowering of the threshold would result in no cases of CRC being missed, but would increase the number of 'unnecessary' colonoscopies from 198 to 548 (see *Figure 5b*). No study of HM-JACKarc assessed the any detectable Hb threshold for CRC. (Confidential information has been removed.)

No study reported data on the effects of patient age, sex or presenting symptoms, or on the effects of multiple sampling, on the accuracy of faecal immunochemical testing for the target condition of CRC. However, the results of multivariable regression analyses indicate that participant age[73] and sex,[53,73] but not presenting symptoms (NICE and SIGN 2-week referral criteria),[53] as well as faecal Hb concentration,[53,73] are independent predictors of CRC. Validation of the FAST score (Cubiella *et al.* 2016;[127] Callum Fraser, personal communication), which incorporates age, sex and faecal Hb concentration, has suggested that a score threshold of 2.12 (range of score not reported) can be used to reliably rule out CRC (sensitivity 100%, 95% CI 97.7% to 100%); however, the specificity of the score is very low (19.8%, 95% CI 18.6 to 21.1%) at this threshold.

If a lower diagnostic threshold is applied, that is, the target condition includes HRA as well as CRC (advanced neoplasia), then the rule-out performance of all FIT methods is reduced. For faecal immunochemical testing based on a single faecal sample and a threshold of 10 µg Hb/g faeces, the sensitivity estimates indicated that neither a negative OC-Sensor nor a negative HM-JACKarc FIT would be likely to be considered adequate to rule out CRC; the summary estimate of sensitivity for OC-Sensor was 62.9% (95% CI 55.9% to 69.4%), based on three studies, and the estimate of sensitivity for HM-JACKarc was 70.0% (95% CI 50.6% to 85.3%), based on one study.[56] The corresponding specificity estimates were 84.6% (95% CI 82.8% to 86.2%) and 77.8% (95% CI 73.8% to 81.4%), respectively. One additional study[57] reported sensitivity and specificity estimates for HM-JACKarc at the 10 µg Hb/g faeces threshold and any detectable Hb thresholds; however, this study[57] differed from others in the systematic review in that it included some patients who were undergoing colonoscopy for polyp surveillance and excluded people with GI bleeding or active rectal bleeding; the prevalence of CRC in this study was the lowest of any included study (0.96%).[57] When a hypothetical cohort of 1000 patients is considered, assuming that prevalence estimates have been derived from the included studies, the estimated number of HRA cases that would be missed using either of the two FIT assays (OC-Sensor and HM-JACKarc at the 10 µg Hb/g faeces threshold) is 40 and 22, respectively; under the same assumptions the number of 'unnecessary' colonoscopies carried out on people without CRC would be 157 and 205, respectively (see *Chapter 3*, *Results of the assessment of clinical effectiveness assessment*, *Figures 7a* and *10*). (Confidential information has been removed.) Using the OC-Sensor assay and a threshold of any detectable Hb increased the summary estimate of sensitivity to 84.1% (95% CI 78.3% to 88.8%), with a corresponding specificity estimate of 45.2% (95% CI 42.7% to 47.7%). For the hypothetical cohort of 1000 patients, this lower threshold would still result in 18 cases of HRA being missed and 485 'unnecessary' colonoscopies being conducted in people without HRA or CRC (see *Figure 7a*).

Only the Auge *et al.* study[57] reported any data on the effects of patient characteristics (sex) and number of faecal samples tested on the accuracy of faecal immunochemical testing for the target condition of advanced neoplasia. However, the results of multivariable regression analyses indicate that participant age[53,73] and sex,[53,73] but not presenting symptoms (NICE and SIGN 2-week referral criteria),[53] as well as faecal Hb concentration,[53,73] are independent predictors of advanced neoplasia. Validation of two risk scores based on the analyses (both incorporating age, sex Hb concentration) gave increased estimates of sensitivity and specificity. One study reported sensitivity and specificity estimates of 88.1% (95% CI 74.3% to 96.0%) and 63.3% (95% CI 57.4% to 69.0%), for a threshold of '5' on a score with a scale of 0–11.[53] The FAST score (Cubiella *et al.* 2016;[127] Callum Fraser, personal communication) threshold of 2.12 (range of score not reported) gave sensitivity and specificity estimates of 96.7% (95% CI 94.9% to 98.0%) and 21.5% (95% CI 20.1% to 22.9%). These data suggest that risk scores may have the potential to provide a more reliable rule-out method than faecal immunochemical testing alone at lower thresholds of disease.

No studies were identified which assessed the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients, and no studies were identified which directly compared the performance of different FIT assays, or which compared one or more FIT assays with a gFOBT method.

The selection of FIT accuracy data for use in cost-effectiveness modelling was based on the optimal threshold (maximum sensitivity and specificity) for each assay method and the threshold required to provide optimal rule-out performance (highest sensitivity and lowest number of cases missed). Because no studies

were identified which directly compared the performance of one or more FIT assays with a gFOBT method, accuracy data for gFOBT that were used in the base case for cost-effectiveness modelling were those used in the NG12 model.[6] The primary study from which these data were taken, Gillberg *et al.*,[91] was a retrospective study using a Swedish cancer registry, in which a diagnosis of CRC was classified as any diagnosed CRC within 2 years of guaiac faecal occult blood testing. It was unclear whether or not all of the patients included in the study had been symptomatic at the time of guaiac faecal occult blood testing, and the prevalence of CRC, in the subgroup of study participants used to provide accuracy data for the model, was very low (0.36%); the prevalence of CRC for the whole population of the Gillberg *et al.* study[91] (1.8%) was closer to the prevalence estimate that was used in the NG12 model[6] (1.5%). Because of these problems with the Gillberg *et al.* study[91] data, we chose to conduct scenario analyses using published estimates of gFOBT accuracy in symptomatic patients obtained from studies that were identified during the process of inclusion screening for our systematic review: the Niv and Sperber[92] and Bjerregaard *et al.*[93] studies. Both of these studies were conducted in symptomatic patients and the prevalence of CRC was 2.5% and 3.1%, respectively, making these studies closer to the population defined for this assessment.

Cost-effectiveness

We assessed the cost-effectiveness of using quantitative faecal immunochemical tests for Hb (faecal immunochemical testing) as a triage test for people presenting, in primary care settings, with lower abdominal symptoms who are at low risk for CRC according to the criteria defined in NG12.[1] Our review of economic analysis found no papers or reports assessing specifically this decision problem. The most relevant study was the one conducted in NG12,[6] which estimated the cost-effectiveness of five different investigations (i.e. faecal occult blood testing, barium enema, flexible sigmoidoscopy, CTC or colonoscopy) for suspected CRC ordered in primary care for patients aged 40 years and over with a change in bowel habit as the main symptom. This study was used to guide a part of the development of our diagnostic assessment model.

Diagnostic accuracy of faecal immunochemical testing was captured in the model using data on sensitivity and specificity for the detection of CRC using a single faecal sample obtained from our systematic review. For the base-case scenario, we considered a threshold of 10 µg Hb/g faeces or equivalent. For this threshold, our systematic review obtained data only for OC-Sensor and HM-JACKarc. The comparators chosen for this diagnostic assessment were gFOBTs and no triage (referral straight to colonoscopy). For gFOBT, we considered the sensitivity and specificity estimates used in NG12[1] (base-case scenario) and in two papers identified in our systematic review (scenario analyses) that were thought to represent a better match for the population that was specified for this diagnostic assessment. Additionally, the FOB Gold FIT system was included as an intervention in scenario analyses, despite the limitations of the accuracy data found in our systematic review, as described in *Chapter 3*.

The base-case cost-effectiveness results suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the 'no triage' strategy (referral to colonoscopy) is the most expensive. Overall, faecal immunochemical testing was cost-effective when compared with no triage. This was either because the latter was dominated (less effective and more costly) or because the ICERs obtained were high, but in the south-west quadrant of the cost-effectiveness plane, that is, faecal immunochemical testing was slightly less effective, but cheaper, than no triage. In this case the cost savings could be said to 'outweigh' the slight loss in QALYs. When the comparator was gFOBT, the cost-effectiveness results showed that faecal immunochemical testing was more effective and more costly than gFOBT, but the ICERs obtained were below the common threshold ICER of £30,000, and thus the interventions can also be considered cost-effective. However, it should be noted that the PSA results showed that this finding should be interpreted with caution. Because the PSA outcomes were scattered over the four quadrants of the cost-effectiveness plane in an asymmetrical fashion, gFOBT had in general a high probability of being cost-effective (especially at low values of the ICER threshold) and sometimes gFOBT was the strategy with the highest probability of being cost-effective.

The results of the different scenario analyses did not differ substantively from the base-case results. The scenarios for which the accuracy estimates for gFOBT were based on the studies by Niv and Sperber[92] and Bjerregaard *et al.*[93] (those that are considered more representative of the population of this diagnostic assessment) were more favourable than the base-case scenario with regard to the interventions. In only two scenarios would FIT strategies be considered to be not cost-effective because the ICER exceeded the £30,000 threshold. The highest ICER was obtained when OC-Sensor was compared with gFOBT when a threshold of any detectable Hb was assumed for this FIT assay (£65,192). This was expected, as reducing the threshold for FIT results in the test being less effective in avoiding colonoscopies, that is, this threshold is associated with the highest number of FPs. When HM-JACKarc was compared with gFOBT in the scenario with high mortality due to colonoscopy, the ICER was £45,271.

Strengths and limitations of assessment

Clinical effectiveness

Extensive literature searches were conducted in an attempt to maximise retrieval of relevant studies. These included electronic searches of a variety of bibliographic databases, as well as screening of clinical trials registers and conference abstracts to identify unpublished studies. Because of the known difficulties in identifying test accuracy studies using study design-related search terms,[128] search strategies were developed to maximise sensitivity at the expense of reduced specificity. Thus, large numbers of citations were identified and screened, relatively few of which met the inclusion criteria of the review.

The possibility of publication bias remains a potential problem for all systematic reviews. Considerations may differ for systematic reviews of test accuracy studies. It is relatively simple to define a positive result for studies of treatment, for example a significant difference between the treatment and control groups, which favours treatment. This is not the case for test accuracy studies, which measure agreement between index test and reference standard. It would seem likely that studies finding greater agreement (high estimates of sensitivity and specificity) will be published more often; however, the relative priorities given to sensitivity and specificity estimates may vary depending on the intended application of the test. In addition, test accuracy data are often collected as part of routine clinical practice, or by retrospective review of records; test accuracy studies are not subject to the formal registration procedures applied to RCTs and are therefore more easily discarded when results appear unfavourable. The extent to which publication bias occurs in studies of test accuracy remains unclear; however, simulation studies have indicated that the effect of publication bias on meta-analytic estimates of test accuracy is minimal.[129] Formal assessment of publication bias in systematic reviews of test accuracy studies remains problematic and reliability is limited.[39] We did not undertake a statistical assessment of publication bias in this review. However, our search strategy included a variety of routes to identify unpublished studies and resulted in the inclusion of a number of conference abstracts.

Despite our extensive searches, no studies were identified that assessed the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients. We identified one article that assessed the performance of Hb/Hp complex in faeces for detecting CRC; the reported sensitivity and specificity estimates were 77% and 95%, using a threshold of 2 µg/g faeces.[130] The test manufacturer stated, of this study, that: 'My understanding is that all of the patients were symptomatic' (e-mail from Andrea Lennerz, R-Biopharm AG, Germany, via Rebecca Albrow, NICE, to Marie Westwood, KSR Ltd, 27 May 2016, personal communication). However, this study did not meet the inclusion criteria for our systematic review, as it used an early developmental immunoluminometric assay for Hb/Hp complex and not an assay that is currently commercially available or in use in a NHS laboratory.

No studies were identified which directly compared the performance of different FIT assays, or which compared one or more FIT assays to a gFOBT method; therefore, all of the data included in this assessment refer to the clinical effectiveness of individual FIT methods and *not* to their comparative effectiveness.

Although gFOBT was not one of the interventions included in our systematic review, it was considered to be a comparator for cost-effectiveness modelling. In order to inform cost-effectiveness modelling, our searches therefore included general terms for faecal occult blood testing and guaiac faecal occult blood testing. Diagnostic accuracy studies of gFOBT conducted in symptomatic patients, retrieved by these searches, were identified during the systematic review process. However, we do not consider that we have conducted a full systematic review of guaiac faecal occult blood testing in symptomatic patients, as our searches did not include terms for gFOBT product names and our inclusion criteria specified only those studies of gFOBT that included a comparison to one or more FIT methods.

Clear inclusion criteria were specified in the protocol for this review, a copy of which is available online (www.nice.org.uk/guidance/GID-DG10005/documents/final-protocol). The eligibility of studies for inclusion is therefore transparent. In addition, we have provided specific reasons for exclusion for all of the studies which were considered potentially relevant at initial citation screening and were subsequently excluded on assessment of the full publication (see *Appendix 4*). The review process followed recommended methods to minimise the potential for error and/or bias;[37] studies were independently screened for inclusion by two reviewers, and data extraction and quality assessment were undertaken by one reviewer and checked by a second (MW and SL). Any disagreements were resolved by consensus.

All of the studies included in this review were assessed for risk of bias and applicability using the QUADAS-2 tool,[45] which is recommended by the Cochrane Collaboration.[39] QUADAS-2 is structured into four key domains: participant selection, index test, reference standard and the flow of patients through the study (including timing of tests). Each domain is rated for risk of bias (low, high or unclear); the participant selection, index test and reference standard domain are also separately rated for concerns regarding the applicability of the study to the review question (low, high or unclear). The results of the QUADAS-2 assessment are reported, in full, for all of the included studies in *Appendix 3* and are summarised in *Chapter 3* (see *Study quality*). Those studies that reported development of risk scores, in addition to test accuracy data, were also assessed using the PROBAST tool.[46] PROBAST has been designed to assess both the *risk of bias* and *concerns regarding applicability* of a study that evaluates (develops and/or validates) a multivariable diagnostic or prognostic prediction model. It has a domain-based structure, similar to that of QUADAS-2, and is intended to be used for the assessment of primary studies that are included in a systematic review. PROBAST is not yet published, but has been used with the consent of the steering group, of which the lead author of this assessment report is a member.

This assessment includes information on the development and validation of risk scores that incorporate faecal Hb levels measured by faecal immunochemical testing, as well as test accuracy data for faecal immunochemical testing alone. Available data on the performance characteristics of such scores have been included in order to inform the question of whether or not the performance characteristics of faecal immunochemical testing can be improved by using it as part of a simple scoring system that includes other information that is readily available to medical practitioners.

All of the studies included in our systematic review were conducted in Europe; however, only four studies[13,52,56,75] were conducted in the UK (one in England[75] and three in Scotland[13,52,56]). Given that population studies have shown variation in faecal Hb concentrations, and hence potential variation in optimal thresholds for faecal immunochemical testing, across different geographic location,[88,89] this may limit the applicability of our findings to UK settings. In addition, the definitions of HRA used in UK studies are generally based on number and size of lesions, as per BSG guidelines,[90] whereas those conducted in mainland Europe have used definitions that also include morphology. However, it should also be noted that validation data for the FAST score (Callum Fraser, personal communication) indicated that there was no significant difference in the sensitivity of the tool (for either CRC or advanced neoplasia) between Scotland and Spain, the two countries where the majority of studies in our systematic review were conducted.

Although the sample sizes of studies included in our systematic review were generally large for diagnostic accuracy studies (median $n = 474$, range 83–2058), it should be noted that study samples may not be

representative of all of those people presenting in primary care with symptoms as specified in NG12.[1] Only three of the studies[13,52,56] included in our systematic review explicitly reported the number of people who were invited to participate, and proportions agreeing were relatively low (64%,[13] 56%[56] and 48%[52]), implying that study samples may be self-selecting for more motivated patients.

A further limitation of the study populations is that no study reported data that were specific to the population that was defined in the scope for this assessment (people presenting, in primary care settings, with lower abdominal symptoms who are at low risk for CRC according to the criteria defined in NG12[1]). Only one study[52] was conducted in a primary care setting, and this study reported that faecal immunochemical testing was ordered by GPs at the point of referral to secondary care. Although the primary care study might be considered the most applicable to this setting, because it is the only study to allow a change in referral decision based on FIT result, this design also gives rise to a risk of bias, as 11% of participants who returned a FIT sample were excluded from the analysis because they were not subsequently referred to secondary care or the referral was cancelled.[52] All of the studies included some participants who had symptoms that may be considered to be associated with a higher probability of CRC and which are components of the criteria for 2-week referral as defined in NG12[1] (e.g. rectal bleeding). The prevalence of CRC and advanced neoplasia is likely to differ with different presenting symptoms and with the health-care setting in which testing is undertaken (primary care vs. secondary care); the median prevalence of CRC reported in the studies included in our systematic review was 3.0% (range 1.0–12.3%) compared with the estimate of 1.5% for the relevant symptomatic group used in NG12.[6] Although it is known that the prevalence of the target condition can affect test performance characteristics,[7] there are insufficient data to adequately assess these effects for the use of faecal immunochemical testing in symptomatic patients. The results of our systematic review do not suggest significant differences in test performance between the primary care study[52] and other included studies that used the same FIT assay, threshold(s) and target condition (see *Chapter 3*, *Diagnostic performance of the OC-Sensor faecal immunochemical test assay*). Similarly, validation data for the FAST score (Callum Fraser, personal communication) indicated that there was no significant difference in the sensitivity or specificity estimates for the score between primary and secondary care settings.

Systematic reviews conducted previously have assessed the test characteristics of various FIT assays in screening settings[8,131] and compared the performance of faecal immunochemical testing for CRC screening with that of gFOBT.[24,25] However, given the potential for target condition prevalence to affect test performance characteristics,[7] it is important to determine the diagnostic accuracy of faecal immunochemical testing in the population of interest; we are not aware of any previous systematic review on this topic. We identified one large systematic review[132] that assessed the value of symptoms and additional diagnostic tests for CRC, used in symptomatic patients in primary care. However, the searches for this review were completed in 2008 and identified only three studies of quantitative FIT assays. Our searches identified all of the three studies:[133–135] one study[133] was excluded from this assessment because it included a mixed population of symptomatic, screening and high-risk patients and no separate data for the symptomatic subgroup, and the remaining two studies[134,135] were excluded because they used development stage Hb/Hp complex tests, which are not currently available in the NHS. Additionally, Williams *et al.*[136] have recently published a systematic review of risk prediction models for CRC or HRA in people with symptoms. This review[136] included 15 risk models, none of which included faecal Hb measured by faecal immunochemical testing (or any other method) as a variable. Our systematic review is the first to assess the performance of faecal immunochemical testing, as a triage test for CRC, in people with symptoms and to consider the potential utility of applying faecal immunochemical testing as part of a simple risk score.

Cost-effectiveness

A major strength of our analysis is that it is the first study to assess the cost-effectiveness of faecal immunochemical testing as a triage test for symptomatic low-risk people presenting in primary care settings, based on a systematic review of the accuracy of faecal immunochemical testing. The input parameters used to model the accuracy of faecal immunochemical testing in the diagnostic part of the cost-effectiveness model (decision tree) were informed by a comprehensive high-quality systematic literature review on the clinical effectiveness of several FIT assays. For consistency, we sourced costs

(other than those for faecal immunochemical testing and gFOBT) and CRC natural progression parameters from the current clinical guideline NG12.[6] These parameters were updated to their most recent values when deemed necessary. Although many of the input parameters of our cost-effectiveness model are the same as those described in NG12,[6] the ones pertaining to faecal immunochemical testing differed because we performed cost-effectiveness analyses for specific FIT assays. In NG12,[6] faecal immunochemical testing was included only as a single intervention and only in a scenario analysis.

A further strength of our study is that it includes detailed data on resource use and equipment costs for faecal immunochemical testing. Data on resource use were obtained from expert opinion (e-mail from Callum Fraser, NHS Tayside, to Marie Westwood, KSR Ltd, 19 July 2016, personal communication). This was important because figures on resource use for the population considered in this diagnostic assessment are scarce in the literature; we could not find any published study. Data on equipment costs were obtained from the relevant companies and are presented in a detailed and transparent way in this diagnostic assessment. This was also important because, in the papers found, which assessed the costs of faecal immunochemical testing, it was not always clear how the total costs were estimated from resource use and equipment costs.

Finally, we have considered a large variety of scenarios to explore the uncertainties around the assumptions that were made in the cost-effectiveness model and, in order to quantify these uncertainties in a statistical way, we performed PSAs for all of them.

The secondary care aspects of our model are a simplification of what actually occurs in practice. The 'no triage' comparator arm would be more accurately described as 'no FIT/gFOBT', as the secondary care consultation with a gastroenterologist clearly forms part of the triage before colonoscopy. The model structure follows a similar approach to that used in NG12,[6] in that it assumes that all of the patients with a positive FIT/gFOBT and all of the patients in the 'no FIT/gFOBT' arm receive colonoscopy. However, the alternative would involve trying to estimate the proportion of patients whom the gastroenterologist would refer for colonoscopy without faecal immunochemical testing/gFOBT (this proportion would apply to the 'no FIT/gFOBT' arm). We would also need to estimate the effect that the positive FIT/gFOBT result has on the gastroenterologist's probability of requesting colonoscopy (numbers referred from the FIT/gFOBT-positive pathway). We are not aware of any published data to inform these parameters, and asking clinicians for estimates of their own performance (the accuracy of their referral decisions) has a high risk of bias.

There is a potential problem with the population, which is based on NG12,[6] in that it is likely to be heterogeneous, such that many patients might better be treated with a watchful waiting strategy rather than being referred immediately to secondary care. The model assumes that all of the patients who present with the symptoms specified in NG12[6] would be treated in the same way by the GP. Hence, we cannot capture the role of the GP's clinical judgement in ruling out other possible explanations for the presenting symptoms for which faecal immunochemical testing/gFOBT would not be helpful. In practice, this is may be less of a problem than it appears, as the evidence from our systematic review is in a clinically appropriate population (those for whom the GP is considering referral to secondary care or for whom a referral decision has already been made). The prevalence of CRC in this population is also uncertain; NG12[6] relied on expert opinion to provide an estimate, which was 1.5%. In the absence of any data that were specific to this population, we also chose this value for the base case, although we tested the effect of using prevalence as observed in the accuracy studies from our systematic review.

There is a potential for patients with a FIT FP test for CRC to benefit from referral to secondary care/colonoscopy for diagnosis and treatment of conditions other than CRC (see *Chapter 5*, *Clinical effectiveness*). This is not captured in our model, which is, therefore, likely to underestimate the cost-effectiveness of faecal immunochemical testing.

The limitations described for clinical effectiveness regarding the lack, or the poor quality, of accuracy data for the different FIT assays are also applicable to the assessment of cost-effectiveness. Accuracy data were not available for all of the relevant FIT methods and there were no studies that compared more than one FIT method or that compared faecal immunochemical testing with gFOBT.

We lacked data to inform the parts of the diagnostic model that followed a FIT or gFOBT negative result. Therefore, we assumed that those who have CRC would remain symptomatic and would be diagnosed using colonoscopy or CTC. However, we did not know how many non-patients with CRC would also remain symptomatic; hence, we sought expert opinion. We also had to seek expert opinion on the number of patients who would get a second FIT/gFOBT, as well as the time to diagnosis of CRC. We did not seek expert opinion on the accuracy of a second FIT/gFOBT, even though we had no data, because we believe that this is something that cannot be reliably estimated by a clinician. We therefore sent out a questionnaire to 10 specialists, five of whom returned it, although not all of the questions were completely answered. We also conducted scenario analyses on the proportion who were symptomatic and time to diagnosis.

In the absence of data for this population, the probability of undergoing colonoscopy, as opposed to CTC, was estimated to be 83% by the experts (four answers). However, this value seems to be low compared with the screening population. Logan *et al.*[126] found that, for approximately 98% of the screening patients with an abnormal test result, the first investigation was colonoscopy. However, the ratio of colonoscopy to CTC seems to vary by centre and ranges from 0.3% to 9.1%;[137] therefore, this parameter was varied in the scenario analysis.

In the base-case scenario, we assumed that adverse event rates for CTC were the same as those for colonoscopy. However, Burling *et al.*[19] reported that perforation rates for colonoscopy are four times higher than for CTC. No death events were reported and the proportion of patients experiencing bleeding after examination was not described. Thus, it is likely that our assumption would result in an overestimation of the total number of adverse events. Nevertheless, as there is uncertainty around the appropriate estimates for these adverse events, we decided to keep this assumption and interpret it as a worst-case scenario regarding the total number of adverse events. We explored the impact of this assumption on the cost-effectiveness results by performing additional scenario analyses.

Cost estimates for faecal immunochemical testing and gFOBT reported in the literature vary significantly. In particular, the costs of faecal immunochemical testing found in the literature ranged from £1.96 to £10.23 per test, and from (confidential information has been removed) to £9.57 per gFOBT. The estimated costs for the OC-Sensor and the HM-JACKarc FIT assays used in this diagnostic assessment were £4.53 and £6.04, respectively. Although the cost estimates used in this diagnostic assessment are properly reported, we acknowledge that there is uncertainty around the underlying assumptions leading to them. For example, it can be seen that, in *Table 32*, information for certain costs categories is missing. This may lead to an underestimation of the cost estimates for faecal immunochemical testing. On the other hand, the manufacturers indicated that the prices provided were also subject to discount, which could imply a lower cost in practice. Ideally, training and staff costs should have been included for faecal immunochemical testing and gFOBT. However, information about training and staff costs is scarce and, when available, relates to dedicated service provision for the national screening programme. For this reason, we decided not to include these costs in our health economic model. Nevertheless, as FIT assays use automated immunoassay platforms, which are standard in clinical laboratories, we believe that training costs would be minimal. To overcome these limitations, we performed threshold analyses on the cost differences between tests.

Our diagnostic model did not include reduction in quality of life (disutilities) for the adverse events that are associated with colonoscopy. Although no evidence was found on the effects of bleeding and perforation on quality of life, some effects on quality of life might be expected. Nevertheless, as these events are often of short duration, the effects on quality of life can be assumed negligible. Kapidzic *et al.*[138] also reported a slight reduction in quality of life for participants in a screening programme who had a positive result.

This was due to the anxiety of knowing that they tested positive. However, these anxiety episodes can also be assumed to be of short duration, with minimal effects on overall quality of life.

As mentioned in *Chapter 3* (see *Methods of analysis/synthesis*), the sensitivity and specificity point estimates for the OC-Sensor assay were derived using the bivariate model, which accounts for the correlation between sensitivity and specificity. However, in the PSA, sensitivity and specificity were sampled independently from the beta distributions presented in *Table 23*. Thus, the PSA does not account for the correlation between sensitivity and specificity. This was a pragmatic choice, as insufficient data were available to allow an analysis accounting for correlation for the HM-JACKarc or the FOB Gold assays.

The effect of a delayed CRC diagnosis was assumed to be mediated through the probability of progression within Dukes' states, for undiagnosed patients, given a delay in the base case of 6 months. This was because the proportion of patients per Dukes' stage for 6 months seemed to match reasonably well with the idea that FN patients would remain symptomatic and thus be picked up well within 1 year. Estimates for delayed diagnosis were also obtained from clinical experts, although only three of the experts who received our questionnaire answered this question; expert estimates were even lower, with two of them estimating a delay of approximately 2–3 months, whereas the third expert estimated this at between 1 and 2 months. A delay of 1 year also seems to be too long because it would result in 45% at Dukes' stage D. This was deemed too high, given that the initial proportion of patients at stage D was 14%. The only published source that we found reporting delayed diagnosis was the Meester *et al.* study.[139] This study used a microsimulation model to calculate the effect of delay to colonoscopy on an average-risk population cohort in the USA who underwent annual FIT screening (from the age of 50 to 75 years), with follow-up colonoscopy examinations for individuals with positive results in the following 12 months. For the scenario of diagnostic follow-up at 12 months from a positive FIT, diagnosed cancers shifted towards more advanced stages, but still with only 8% in stage D. Regardless of the precise delay and its effect on progression, the cost-effectiveness results did not change significantly assuming 6 months' or 1 year's delay and so we decided not to run an additional scenario for a smaller delay. Note, however, that, as the delay in diagnosis diminishes, the differences in QALYs between the strategies decrease as well. In a hypothetical scenario with no delay, the difference in QALYs will be caused only by mortality. In this situation, the strategy with the least number of colonoscopies (gFOBT) is likely to dominate all of the others.

Colorectal cancer mortality was modelled using observational data by CRC stage at the time of diagnosis from the NCIN,[98] as used in NG12.[6] Patients who survive might eventually progress, thus increasing mortality. It was not clear the extent to which the effect of progression was included. We chose to include a separate estimate of the rate of progression as in NG12.[6] However, the progression probabilities, which were obtained from Tappenden *et al.*,[99] were for undiagnosed patients with CRC. This is an obvious limitation, as diagnosed patients are considered in the model following colonoscopy. We also did not model separately the effect of treatment on patients with CRC mortality or cost, assuming that the estimates of mortality and cost were from all diagnosed patients with CRC, including those who had been treated and indeed 'cured'. This does mean that the effect of newer treatments and thus the effect of delay to diagnosis cannot be taken into account.

Despite the limitations of the model for CRC progression described above, it should be emphasised that the lifetime cost-effectiveness results of this diagnostic assessment are completely determined by the results of the diagnostic part of the economic model. Thus, any difference between the strategies observed in the lifetime results was already captured in the diagnostic phase. Beyond the diagnostic model, the differences between the strategies were very small because these were caused only by the number of CRC-diagnosed patients and the distribution of these between Dukes' stages. Given that death (due to colonoscopy) in the diagnostic phase is almost negligible, we could roughly estimate these as 15 patients with CRC from a hypothetical cohort of 1000 (as the estimated prevalence of the disease is 1.5%). Therefore, any difference in the lifetime results between the strategies will be caused by only these 15 patients. Hence, all of the limitations and uncertainties of the model for CRC progression will have a minimal impact on the model results of this diagnostic assessment. If the disease prevalence, the life expectancy or the costs and benefits

of the treatments and surveillance of the population with the disease are likely to make a difference in the lifetime cost-effectiveness results then all of the limitations of the CRC model should be explored with extra caution.

Finally, we would like to emphasise the importance of specificity on the cost-effectiveness results. This can be partly explained, for example, with simple algebra. As described in *Chapter 4* (see *Model parameters*), the probability that FIT/gFOBT is positive can be calculated as (sensitivity × prevalence) + [(1 – specificity) × (1 – prevalence)]. The first part of this equation (sensitivity × prevalence) is the probability of a TP, that is, of sending patients who will be diagnosed with CRC. The second part [(1 – specificity) × (1 – prevalence)] is the probability of a FP, that is, of wrongly sending healthy patients for colonoscopy. It is clear that in a situation for which the prevalence is low, the weight of specificity on this equation is larger than that of sensitivity, that is, any change in specificity will have a greater effect on the probability of FPs than any change in sensitivity will have on the probability of TPs. In this diagnostic assessment, the prevalence of CRC in the base-case population was assumed to be 1.5%. This means that the probability of a FP can vary from 0 to 0.985, whereas the probability of a TP can vary only from 0 to 0.015. The question then is what are the consequences, in terms of cost and QALYs, of either not missing TPs or avoiding FPs. People without CRC might be subjected to unnecessary colonoscopies, incur unnecessary cost and experience unnecessary adverse events (including death). On the other hand, patients with CRC might receive an earlier diagnosis, resulting in an increased number of QALYs. In fact, there was very little difference in QALYs between the FIT/gFOBT and the 'no triage test', which indicates little difference between avoiding FPs or not missing TPs in terms of health effects. Nevertheless, it appears that, in our model, improved specificity does outweigh improved sensitivity. This was clearly shown by the fact that OC-Sensor was almost identical to 'no triage test' in terms of QALYs, but cheaper, whereas HM-JACKarc, with its higher sensitivity and lower specificity, produced fewer QALYs and was more costly than OC-Sensor. This effect was also observed in the scenario analyses using the estimates of gFOBT accuracy from Niv and Sperber[92] and Bjerregaard *et al.*,[93] where, with respect to the base-case scenario, sensitivity increased more than specificity decreased (approximately 20–25% vs. 9–15%). The net effect of these changes was that the cost-effectiveness results for gFOBT were worse than those obtained in the base-case scenario.

Uncertainties

Clinical effectiveness

There remain a number of areas of uncertainty in relation to the performance characteristics of faecal immunochemical testing in specific patient subgroups and test combinations.

Population data indicate that concentrations of faecal Hb vary with age and sex, being higher in men and the elderly.[88,140] Further, a recent study conducted in Scotland found that faecal Hb concentrations also increased with increasing levels of deprivation (measured using the Scottish Index of Multiple Deprivation) and that this trend remained after controlling for age and sex.[141] Thus, at any cut-off concentration, more men, more older people and more people in high deprivation groups are likely to have a positive result on faecal immunochemical testing. The performance of faecal immunochemical testing in these subgroups, within the symptomatic population, is therefore an important consideration for this assessment; optimal thresholds may differ between subgroups and may also differ depending on the geographic location in which the test is being applied. The baseline characteristics of our included studies (where reported) indicated that the average age of participants ranged from 59 to 67 years (total range was 16–94 years) and the percentage of males ranged from 40.4% to 56%. However, only one of the studies included in our systematic review compared the accuracy of a FIT assay (HM-JACKarc) in men and women,[57] and no study compared different age groups. The study reporting separate data for men and women found that, at all thresholds, the observed sensitivity of HM-JACKarc for advanced neoplasia was higher in men than in women and the observed specificity was similar for men and women.[57] This indicates that, at any given threshold, more women than men with CRC or HRA may be missed by using a FIT as a triage test to determine referral to secondary care. However, it should be noted that this study differed from others in

the systematic review in that it included some patients who were undergoing colonoscopy for polyp surveillance and excluded people with GI bleeding or active rectal bleeding; the prevalence of CRC in this study was the lowest of any included study (0.96%).[57] More data are needed to adequately assess whether or not there are clinically relevant differences in test performance between men and women, and these data are needed for all FIT assays. We did not identify any studies that compared the accuracy of faecal immunochemical testing in different age groups, or with varying levels of deprivation. Validation data for the FAST score (Callum Fraser, personal communication) indicated that there were no significant differences in the sensitivity of this tool between men and women and between patients aged < 50 years and those who were ≥ 50 years old.

The effects on FIT performance of using multiple faecal samples per patient remain unclear. One published study[57] and one unpublished study, Hospital Clinic de Barcelona 2015 (Philippa Pinn, personal communication), included in our systematic review, compared single sampling with double sampling, and both asked participants to collect two consecutive faecal samples. The Auge *et al.* study[57] used HM-JACKarc and reported that sensitivity for advanced neoplasia was increased (at all thresholds) when the highest value from two consecutive FIT samples was used, compared with using only the first sample; in this study, FIT results were discordant in 39.2% of participants. The Hospital Clinic de Barcelona 2015 study (confidential information has been removed). There is currently insufficient information about intra-individual variation in faecal Hb concentration over time to determine the clinical utility of multiple sampling.

The scope of this assessment did not include evaluation of the performance characteristics of faecal immunochemical testing when used in combination with other biomarkers. However, we identified one study[142] that did not meet the inclusion criteria for our systematic review because it used an obsolete FIT assay, but that reported data on the performance characteristics of faecal immunochemical testing in combination with faecal calprotectin, M2-PK or both (for which a positive result was defined as at least one test being positive) for the target conditions of CRC and HRA, as well as data on the performance characteristics of faecal immunochemical testing alone. Faecal calprotectin is an inflammatory marker, whereas M2-PK is a key enzyme in tumour metabolism.[142] This study[142] found that, in all cases, the addition of at least one further test to faecal immunochemical testing resulted in markedly increased sensitivity and decreased specificity. The sensitivity and specificity estimates for faecal immunochemical testing alone and CRC were 61.7% (95% CI 47.4% to 74.2%) and 88.8% (95% CI 84.1% to 92.3%), respectively; for the combination of faecal immunochemical testing and faecal calprotectin these estimates were 90.9% (95% CI 78.8% to 96.4%) and 35.9% (95% CI 29.7% to 42.6%), respectively; for faecal immunochemical testing and M2-PK, sensitivity and specificity were 91.5% (95% CI 80.1% to 96.6%) and 57.1% (95% CI 50.6% to 63.2%), respectively, and, for all of the three markers, they were 95.7% (85.7% to 98.8%) and 24.1% (18.8% to 30.2%), respectively.[142] Although all of the sensitivity estimates were generally lower, this pattern was repeated when the target condition was advanced neoplasia.[142] However, the FIT threshold in this study (20 µg Hb/g faeces) was higher than that which the results of our systematic review indicate is likely to be the optimal threshold (10 µg Hb/g faeces or a lower threshold). A second study[143] of accuracy for the target condition of advanced neoplasia, which did not meet the inclusion criteria for this assessment because it used a qualitative FIT method, also found that combining faecal calprotectin with faecal immunochemical testing (where a positive result was defined as either or both tests positive) resulted in increased sensitivity and decreased specificity [92% (95% CI 82% to 97%) and 49% (95% CI 43% to 54%)] compared with faecal immunochemical testing alone [74% (95% CI 62% to 83%) and 82% (95% CI 78% to 86%)].[143] The effectiveness of combining other biomarkers with quantitative faecal immunochemical testing (at the threshold at which faecal immunochemical testing is likely to be used in practice) remains unclear. We did not identify any data about the effects of adding faecal calprotectin (or any other biomarker) to risk scores that include faecal immunochemical testing. A study provided ahead of publication (e-mail from Karel Moons, University Medical Center, Utrecht, the Netherlands, to Marie Westwood, KSR Ltd, 20 June 2016, personal communication) reported the development of a multivariable diagnostic model for significant colorectal disease (defined as CRC, adenoma of > 10 mm, IBD or diverticulitis). This model included age, symptoms, digital rectal examination, and point-of-care FITs and faecal calprotectin tests. The authors concluded that this model may avoid approximately 30% of colonoscopy referrals from primary care at the cost of delaying

around 6% of diagnoses (mostly HRA or diverticulitis); whether faecal calprotectin adds value, over and above point-of-care FIT was uncertain. Given the trade-off between ease of use/simplicity and diagnostic performance, the clinical value of including additional variables (e.g. symptoms and further diagnostic tests) in risk scores for CRC and/or other significant bowel disease is likely to require further investigation.

There is uncertainty about downstream consequences of using faecal immunochemical testing to triage symptomatic patients in primary care. It can be seen from the findings of our systematic review (see, in *Chapter 3*, the sections relating to the diagnostic performance of the OC-Sensor, HM-JACKarc, FOB Gold and RIDASCREEN FIT assays) that triage using faecal immunochemical testing at thresholds around 10 µg Hb/g faeces has the potential to correctly rule out CRC and avoid colonoscopy in approximately 75% of symptomatic patients and that this estimate does not appear to vary greatly between FIT assays. Further, the relatively high proportion of FIT FPs observed when the target condition is CRC may be mitigated by the detection of other bowel pathologies in these patients; we estimate that between 22.5% and 93% of patients with a positive FIT and no CRC will have other significant bowel pathologies, depending largely on how many, and which, diagnoses are included in the target condition.

The full potential benefits of faecal immunochemical testing in symptomatic patients, including those relating to diagnoses other than CRC, remain unclear. This issue may be particularly important in younger patients, in whom the prevalence of CRC is lowest and other diagnoses are more likely. Our systematic review identified a recently published protocol for a cluster randomised trial (NCT02308384) of a clinical education intervention (provision of a starting package of faecal immunochemical testing with clinical instructions, including guidance on interpretation of results) in general practices in Denmark, which may partially address these issues.[144] The stated aim of this trial is to assess the diagnostic value and clinical implications of using faecal immunochemical testing, in general practice, for patients presenting with non-alarm symptoms of CRC ('low risk, but not no risk'). This population is defined as patients aged ≥ 30 years with symptoms and signs of CRC, but who do not meet the Danish Cancer Patient Pathway referral criteria; typical indications are given as change in bowel habit, abdominal pain, anaemia or decrease in Hb of > 10%, non-specific symptoms (weight loss, fatigue, loss of appetite). The specified outcome measures for clinical impact are age- and sex-standardised number and rate of urgent referrals for CRC; age- and sex-standardised number and rate of colonoscopies; all colonoscopy findings by ICD-10 code; age- and sex-standardised number of CRCs diagnosed; stage distribution of CRC diagnosed (I–IV). This trial has the potential to inform the clinical effectiveness component of this assessment, but will not address all potentially relevant applications of faecal immunochemical testing, as it is designed to assess faecal immunochemical testing as a rule-in test, with all patients who have a positive result (≥ 50 µg/l Hb, equivalent to 10 µg Hb/g faeces using OC-Sensor) receiving urgent colonoscopy referral; interpretation guidance in the protocol states that a negative FIT should not exclude CRC.

Finally, the acceptability of faecal immunochemical testing, as indicated by reported sample return rates, varied widely between the studies included in our systematic review. There is evidence that faecal immunochemical testing is more acceptable, when used as a screening test/method, than gFOBT; the use of faecal immunochemical testing in screening programmes results in increased uptake compared with gFOBT.[145] However, these data are unlikely to be transferable to symptomatic patients, for whom factors such as the setting in which the test is requested, and advice and information received directly from clinicians, will affect uptake rates. It therefore remains unclear whether or not the method of assessing faecal occult blood has any effect on uptake in patients who are symptomatic.

Cost-effectiveness

The main uncertainties described for the review of clinical effectiveness also apply to the assessment of cost-effectiveness. These are caused by a lack of clinical effectiveness data for the performance characteristics of faecal immunochemical testing in specific patient subgroups and for the effects of using multiple faecal samples. Once these uncertainties are resolved, the cost-effectiveness of faecal immunochemical testing could be assessed for different subgroups of patients (e.g. elderly) and faecal immunochemical testing using multiple faecal samples per patient could be included as an intervention in our cost-effectiveness model.

Chapter 6 Conclusions

Implications for service provision

There is evidence to suggest that triage using faecal immunochemical testing, when used at a threshold of 10 µg Hb/g faeces for OC-Sensor or HM-JACKarc, may be sufficient to rule out CRC in symptomatic patients. In addition, the relatively high proportion of FIT FPs observed when the target condition is CRC may be mitigated by the potential to diagnose other bowel pathologies in these patients. There was insufficient evidence to adequately assess the diagnostic performance of FOB Gold in symptomatic patients. No evidence about the diagnostic performance of RIDASCREEN Hb or RIDASCREEN Hb/Hp complex in symptomatic patients was identified. No studies were identified that directly compared the performance of different FIT assays, or that compared one or more FIT assays with a gFOBT method; therefore, the relative effectiveness of different methods of measuring faecal occult blood remains uncertain.

The base-case cost-effectiveness results suggested that the difference in QALYs between all of the strategies included in this assessment is minimal and that the 'no triage' strategy (referral to colonoscopy) is the most expensive. Overall, faecal immunochemical testing appeared to be cost-effective when compared with no triage or gFOBT. The results of the different scenario analyses did not differ substantively from the base-case results. However, the scenarios for which the accuracy estimates for gFOBT were based on studies that were considered to be more representative of the population of this diagnostic assessment were more favourable than the base-case scenario with regard to faecal immunochemical testing. The results of our analysis suggest that faecal immunochemical testing could provide a cost-effective (cost-saving) triage option for patients whose symptoms are not considered high risk for CRC.

Suggested research priorities

Further, large diagnostic cohort studies are needed to fully evaluate the performance of quantitative faecal immunochemical testing in the setting (primary care) and population (symptomatic patients who are at low risk of CRC, as defined in NG12[1]) specified in the scope for this assessment. Studies comparing the performance of different FIT assays are also needed; such studies should be direct comparisons, involving patients providing multiple samples from a single bowel movement.

If adoption of the FOB Gold, RIDASCREEN Hb or RIDASCREEN Hb/Hp complex is to be considered, studies are needed to evaluate the diagnostic accuracy of these tests in symptomatic patients and to determine optimal thresholds.

If FIT is introduced into routine practice in primary care, a post-implementation audit would be valuable. For example, this could be used to investigate the proportion of FIT-negative patients who go on to have a colonoscopy as well as the delay to getting the colonoscopy. This would improve cost-effectiveness modelling, given that these two parameters had to be estimated using expert opinion. In addition, patients could be followed up to measure mortality and progression, particularly as, as in NG12,[6] the cost-effectiveness analysis relied on data on progression from those who were undiagnosed.

Studies comparing the effectiveness of different approaches to safety netting in patients who have negative FIT results may be useful in optimising care pathways.

Multivariable prediction modelling studies may be useful to assess the independent predictive value of a positive FIT result, in the context of other clinical risk factors and tests. This approach may be considered to be the most efficient method of capturing the effects of clinical judgement. Prediction modelling studies

should consider the trade-off between the potential for improved model performance and ease of use (the extent to which the components of any risk score developed are readily available to GPs).

Studies that are designed to capture the full potential benefits of faecal immunochemical testing in symptomatic patients, including those relating to diagnoses other than CRC, are likely to be informative. This issue may be particularly important in younger patients, among whom the prevalence of CRC is lowest and other diagnoses are more likely. An example of such a study might be a cluster RCT, in which primary care practices are randomised to use FIT triage in the relevant patient group or refer all patients in the relevant symptomatic group to secondary care; outcomes could include urgent referral rates, colonoscopy rates and all diagnoses at colonoscopy.

Further diagnostic cohort studies, or subgroup analyses of existing data sets, are needed to fully explore the possible variation in the accuracy of FIT assays and optimal thresholds in relevant subgroups, for example sex and age.

Studies exploring the diagnostic accuracy of faecal immunochemical testing using multiple samples and faecal immunochemical testing in combination with other biomarkers (e.g. faecal calprotectin or M2-PK), sequential testing using faecal immunochemical testing and other biomarkers, as well as comparisons between faecal immunochemical testing and other biomarkers, may also be of value.

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Marie Westwood planned and performed the systematic review and interpretation of evidence.

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Lisa Stirk devised and performed the literature searches and provided information support to the project.

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Nigel Armstrong contributed to planning and interpretation of the systematic review and cost-effectiveness analyses, and the acquisition of input data, and conducted the model peer review.

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All parties were involved in drafting and/or commenting on the report.

Data sharing statement

This is a systematic review and, therefore, all extracted data are included in the report. Further information can be obtained from the corresponding author.

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Appendix 1 Literature search strategies

Clinical effectiveness searches

MEDLINE (via Ovid): 1946 to March Week 3 2016

Date searched: 30 March 2016.

Records found: 3198.

1. ((immunochem$ or immuno-chem$ or immunohistochem$ or immuno-histochem$ or immunol$ or immunochromatographic or immuno-chromatographic or immunoassay or immuno assay) adj4 (f?ecal or f?eces or stool or stools)).ti,ab,ot,hw. (910)
2. iFOBT.ti,ab,ot,hw. (83)
3. 1 or 2 (932)
4. F?ecal h?emoglobin.ti,ab,ot,hw. (94)
5. H?emoccult.ti,ab,ot,hw. (669)
6. FOBT.ti,ab,ot,hw. (1013)
7. (guaiac$ or gFOBT).ti,ab,ot,hw. (3444)
8. Guaiac/ (319)
9. or/4-8 (4898)
10. (f?ecal or f?eces or stool or stools).ti,ab,ot,hw. (246,345)
11. occult blood/ or occult blood.ti,ab,ot,hw. (6307)
12. (test$ or measur$ or screen$ or exam$).ti,ab,ot,hw. (6,577,832)
13. 10 and 11 and 12 (3172)
14. 3 or 9 or 13 (7254)
15. exp colorectal neoplasms/ (162,552)
16. exp cecal neoplasms/ (4892)
17. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (199,488)
18. CRC.ti,ab,ot. (13,848)
19. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1846)
20. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1675)
21. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (26)
22. 15 or 16 or 17 or 18 or 19 or 20 or 21 (208,172)
23. 14 and 22 (3206)
24. (FOB gold$ or FOBgold$).ti,ab. (11)
25. (jack-arc$ or jackarc$ or HM-JACKarc$).ti,ab. (0)
26. (RIDASCREEN$ H?emo$ or RIDASCREEN$ Hapto$).ti,ab. (1)
27. (OC Sensor$ or OC-Sensor$ or OC Pledia$ or OC-Pledia$).ti,ab. (38)
28. or/24-27 (43)
29. 23 or 28 (3208)
30. exp animals/ not (exp animals/ and humans/) (4,205,567)
31. **29 not 30 (3198)**

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via Ovid): March 29, 2016

Date searched: 30 March 2016.

Records found: 255.

1. ((immunochem$ or immuno-chem$ or immunohistochem$ or immuno-histochem$ or immunol$ or immunochromatographic or immuno-chromatographic or immunoassay or immuno assay) adj4 (f?ecal or f?eces or stool or stools)).ti,ab,ot,hw. (134)
2. iFOBT.ti,ab,ot,hw. (9)
3. 1 or 2 (138)
4. F?ecal h?emoglobin.ti,ab,ot,hw. (16)
5. H?emoccult.ti,ab,ot,hw. (23)
6. FOBT.ti,ab,ot,hw. (72)
7. (guaiac$ or gFOBT).ti,ab,ot,hw. (321)
8. Guaiac/ (0)
9. or/4-8 (418)
10. (f?ecal or f?eces or stool or stools).ti,ab,ot,hw. (18,710)
11. occult blood/ or occult blood.ti,ab,ot,hw. (302)
12. (test$ or measur$ or screen$ or exam$).ti,ab,ot,hw. (671,105)
13. 10 and 11 and 12 (202)
14. 3 or 9 or 13 (632)
15. exp colorectal neoplasms/ (220)
16. exp cecal neoplasms/ (1)
17. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (14,744)
18. CRC.ti,ab,ot. (2522)
19. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (197)
20. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (40)
21. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (0)
22. 15 or 16 or 17 or 18 or 19 or 20 or 21 (15,079)
23. 14 and 22 (254)
24. (FOB gold$ or FOBgold$).ti,ab. (2)
25. (jack-arc$ or jackarc$ or HM-JACKarc$).ti,ab. (3)
26. (RIDASCREEN$ H?emo$ or RIDASCREEN$ Hapto$).ti,ab. (0)
27. (OC Sensor$ or OC-Sensor$ or OC Pledia$ or OC-Pledia$).ti,ab. (3)
28. or/24-27 (6)
29. 23 or 28 (255)
30. exp animals/ not (exp animals/ and humans/) (3648)
31. **29 not 30 (255)**

MEDLINE Epub Ahead of Print (via Ovid): June 20, 2016

Date searched: 21 June 2016.

Records found: 80.

1. ((immunochem$ or immuno-chem$ or immunohistochem$ or immuno-histochem$ or immunol$ or immunochromatographic or immuno-chromatographic or immunoassay or immuno assay) adj4 (f?ecal or f?eces or stool or stools)).ti,ab,ot,hw. (36)
2. iFOBT.ti,ab,ot,hw. (3)
3. 1 or 2 (37)
4. F?ecal h?emoglobin.ti,ab,ot,hw. (4)
5. H?emoccult.ti,ab,ot,hw. (1)
6. FOBT.ti,ab,ot,hw. (24)
7. (guaiac$ or gFOBT).ti,ab,ot,hw. (77)
8. Guaiac/ (0)
9. or/4-8 (102)
10. (f?ecal or f?eces or stool or stools).ti,ab,ot,hw. (1652)
11. occult blood/ or occult blood.ti,ab,ot,hw. (73)
12. (test$ or measur$ or screen$ or exam$).ti,ab,ot,hw. (131,690)
13. 10 and 11 and 12 (65)
14. 3 or 9 or 13 (156)
15. 15 exp colorectal neoplasms/ (0)
16. exp cecal neoplasms/ (0)
17. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (3630)
18. CRC.ti,ab,ot. (799)
19. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (16)
20. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (12)
21. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (0)
22. 15 or 16 or 17 or 18 or 19 or 20 or 21 (3677)
23. 14 and 22 (80)
24. (FOB gold$ or FOBgold$).ti,ab. (1)
25. (jack-arc$ or jackarc$ or HM-JACKarc$).ti,ab. (0)
26. (RIDASCREEN$ H?emo$ or RIDASCREEN$ Hapto$).ti,ab. (0)
27. (OC Sensor$ or OC-Sensor$ or OC Pledia$ or OC-Pledia$).ti,ab. (5)
28. or/24-27 (5)
29. 23 or 28 (80)
30. exp animals/ not (exp animals/ and humans/) (0)
31. **29 not 30 (80)**

EMBASE (via Ovid): 1974 to 2016 March 29

Date searched: 30 March 2016.

Records found: 5255.

1. Fecal Immunochemical Test/ [EMTREE candidate term 13.1.16] (135)
2. ((immunochem$ or immuno-chem$ or immunohistochem$ or immuno-histochem$ or immunol$ or immunochromatographic or immuno-chromatographic or immunoassay or immuno assay) adj4 (f?ecal or f?eces or stool or stools)).ti,ab,ot,hw. (1630)
3. iFOBT.ti,ab,ot,hw. (164)
4. 1 or 2 or 3 (1672)
5. F?ecal h?emoglobin.ti,ab,ot,hw. (155)
6. H?emoccult.ti,ab,ot,hw. (866)

7. FOBT.ti,ab,ot,hw. (1857)
8. (guaiac$ or gFOBT).ti,ab,ot,hw. (5159)
9. Guaiac/ (696)
10. or/5-9 (7538)
11. (f?ecal or f?eces or stool or stools).ti,ab,ot,hw. (347,542)
12. occult blood/ or occult blood.ti,ab,ot,hw. (11,184)
13. (test$ or measur$ or screen$ or exam$).ti,ab,ot,hw. (9,112,793)
14. 11 and 12 and 13 (5121)
15. 4 or 10 or 14 (11,582)
16. exp colon tumor/ (239,813)
17. exp rectum tumor/ (182,401)
18. exp colon cancer/ (191,557)
19. exp rectum cancer/ (148,462)
20. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (318,031)
21. CRC.ti,ab,ot. (27,205)
22. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (2649)
23. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1929)
24. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (29)
25. or/16-24 (329,839)
26. 15 and 25 (5264)
27. (FOB gold$ or FOBgold$).ti,ab. (27)
28. (jack-arc$ or jackarc$ or HM-JACKarc$).ti,ab. (7)
29. (RIDASCREEN$ H?emo$ or RIDASCREEN$ Hapto$).ti,ab. (2)
30. (OC Sensor$ or OC-Sensor$ or OC Pledia$ or OC-Pledia$).ti,ab. (151)
31. or/27-30 (169)
32. 26 or 31 (5274)
33. animal/ (1,733,374)
34. animal experiment/ (1,919,080)
35. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6,178,883)
36. or/33-35 (6,178,883)
37. exp human/ (16,972,709)
38. human experiment/ (350,478)
39. or/37-38 (16,974,155)
40. 36 not (36 and 39) (4,862,933)
41. **32 not 40 (5255)**

The Cochrane Library (Wiley) (via the internet)

www.cochranelibrary.com/

Date searched: 30 March 2016.

Records found:

- CDSR: Issue 3 of 12, March 2016: 25 records
- DARE: Issue 2 of 4, April 2015: 34 records

- HTA Database: Issue 1 of 4, January 2016: 27 records
- NHS EED: Issue 2 of 4, April 2015: 103 records
- CENTRAL: Issue 2 of 12, February 2016: 446 records.

#1 (immunochem* or "immuno-chem*" or immunohistochem* or "immuno-histochem*" or immunol*) near/4 (f*ecal or f*eces) (237)

#2 iFOBT (14)

#3 "F*ecal h*emoglobin" (15)

#4 H*emoccult (143)

#5 FOBT (247)

#6 gFOBT or guaiac (132)

#7 [mh ^guaiac] (30)

#8 f*ecal or f*eces or stool or stools (9516)

#9 MeSH descriptor: [Occult Blood] this term only (480)

#10 "occult blood" (907)

#11 #9 or #10 (907)

#12 test* or measur* or screen* or exam* (430,115)

#13 #8 and #11 and #12 (683)

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #13 (931)

#15 MeSH descriptor: [Colorectal Neoplasms] explode all trees (6053)

#16 MeSH descriptor: [Cecal Neoplasms] explode all trees (9)

#17 (colorec* or rectal* or rectum* or colon* or sigma* or sigmo* or rectosigm* or bowel* or anal or anus) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumo*r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (12,274)

#18 CRC (1334)

#19 (cecum or cecal or caecum or caecal or il*eoc*ecal or il*eoc*ecum) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumo*r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (99)

#20 "large intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumo*r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (54)

#21 "lower intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumo*r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

#22 #15 or #16 or #17 or #18 or #19 or #20 or #21 (12627)

#23 #14 and #22 (638)

#24 "FOB gold*" or "FOBgold*" (2)

#25 "jack-arc*" or "jackarc*" or "HM-JACKarc*" (0)

#26 "RIDASCREEN* Haemo*" or "RIDASCREEN* Hemo*" or "RIDASCREEN* Hapto*" (0)

#27 "OC Sensor*" or "OC-Sensor*" or "OC Pledia*" or "OC-Pledia*" (16)

#28 #24 or #25 or #26 or #27 (16)

#29 #23 or #28 (638) (CDSR: 25; DARE: 34; HTA: 27; NHS EED: 103; CENTRAL: 446)

International Network of Agencies for Health Technology Assessment Publications

www.inahta.org/publications/

Date searched: 30 March 2016.

Records found: 8.

Search terms	Records found
Faeces	0
Feces	0/2
Faecal	1/2
Fecal	7/20
Guaiac	4/4
Total (before deduplication)	**12**
Total (after deduplication)	**8**

National Institute for Health Research Health Technology Assessment programme

www.nets.nihr.ac.uk/projects?collection=netscc&meta_P_sand=Project

Date searched: 30 March 2016.

Records found: 1.

Search terms	Records found
Faeces	0/3
Feces	0
Faecal	1/13
Fecal	0/3
Guaiac	0
Total (before deduplication)	**1**
Total (after deduplication)	**1**

Aggressive Research Intelligence Facility Reviews Database

www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/ARIF/databases/index.aspx

Date searched: 30 March 2016.

Records found: 17.

Search terms	Records found
Faeces	0/2
Feces	0/1
Faecal	8/23
Fecal	12/20
Guaiac	3/3
Total (before deduplication)	**23**
Total (after deduplication)	**17**

PROSPERO (via internet)

www.crd.york.ac.uk/prospero/

Date searched: 30 March 2016.

Records found: 9.

Search terms	Records found
Faeces	1/9
Feces	2/14
Faecal	1/38
Fecal	8/50
Guaiac	4/4
Total (before deduplication)	**16**
Total (after deduplication)	**9**

ClinicalTrials.gov (via internet)

https://clinicaltrials.gov/

Date searched: 8 March 2016.

Records found: 51.

Search terms	Records found
"faecal immunochemical" OR "fecal immunochemical" OR "faecal immuno-chemical" OR "fecal immuno-chemical" OR iFOBT OR "FOB Gold" OR FOBGold OR JACKarc OR RIDASCREEN OR "OC Sensor" OR "OC Pledia"	51

European Union Clinical Trials Register (via internet)

www.clinicaltrialsregister.eu/ctr-search/search

Date searched: 8 March 2016.

Records found: 1.

Search terms	Records found
"faecal immunochemical" OR "fecal immunochemical" OR "faecal immuno-chemical" OR "fecal immuno-chemical" OR iFOBT OR FOBT OR "FOB Gold" OR FOBGold OR JACKarc OR RIDASCREEN OR "OC Sensor" OR "OC Pledia"	1

International Clinical Trials Registry Platform (via internet)

http://apps.who.int/trialsearch/

Date searched: 8 March 2016.

Records found: 29.

Search terms	Records found
faecal immunochemical OR fecal immunochemical OR faecal immuno-chemical OR fecal immuno-chemical OR iFOBT OR FOB Gold OR FOBGold OR JACKarc OR RIDASCREEN OR OC Sensor OR OC Pledia	29

American Gastroenterological Association – Digestive Disease Week 2011–15

Date searched: 13 April 2016.

Records found: 92.

www.gastrojournal.org/content/ddw_abstracts

2011 DDW Abstract Supplement

www.gastrojournal.org/issue/S0016-5085%2811%29X6001-8

2012 DDW Abstract Supplement

www.gastrojournal.org/issue/S0016-5085%2812%29X6001-3

2013 DDW Abstract Supplement

www.gastrojournal.org/issue/S0016-5085%2813%29X6001-9

2014 DDW Abstract Supplement

www.gastrojournal.org/issue/S0016-5085%2814%29X6001-4

2015 DDW Abstract Supplement

www.gastrojournal.org/issue/S0016-5085%2815%29X6001-X

Search terms	2011	2012	2013	2014	2015	TOTAL
"faecal immunochemical"	1	5	0	2	3	
"fecal immunochemical"	9	7	14	16	15	
"faecal immuno-chemical"	0	0	0	0	0	
"fecal immuno-chemical"	0	0	0	0	0	
iFOBT	4	0	3	1	10	
"FOB Gold"	0	0	0	0	0	
FOBGold	0	0	0	0	0	
JACKarc	0	0	0	0	0	
RIDASCREEN	0	0	0	0	0	
"OC Sensor"	0	1	0	0	0	
"OC Pledia"	0	0	0	0	0	
TOTAL (after deduplication)	**14**	**14**	**17**	**19**	**28**	**92**

Annual Meeting of the American Association for Clinical Biochemistry and Laboratory Medicine 2011–15

Date searched: 13 April 2016.

Records found: 3.

www.aacc.org/science-and-research/annual-meeting-abstracts-archive

2011 AACC Annual Meeting

www.aacc.org/~/media/files/annual-meeting/2011/aacc_11_fullabstract.pdf?la=en

2012 AACC Annual Meeting

www.aacc.org/~/media/files/annual-meeting/2012/aacc_12_abstractbookfinalcomplete.pdf?la=en

2013 AACC Annual Meeting

www.aacc.org/~/media/files/annual-meeting/2013/aacc_13_abstractbook_complete.pdf?la=en

2014 AACC Annual Meeting

www.aacc.org/~/media/files/annual-meeting/2014/abstracts/aacc_14_abstractbook_1_combined.pdf?la=en

2015 AACC Annual Meeting

www.aacc.org/~/media/files/annual-meeting/2015/abstracts-2/aacc2015_abstractbook_final_completer1.pdf?la=en

Search terms	2011	2012	2013	2014	2015	TOTAL
faecal immunochemical	0	0	0	0	0	
fecal immunochemical	1	0	0	1	0	
faecal immuno-chemical	0	0	0	0	0	
fecal immuno-chemical	0	0	0	0	0	
FIT	1	0	0	1	0	
iFOBT	0	0	0	0	0	
FOB Gold	0	0	1	1	0	
FOBGold	0	0	0	1	0	
JACKarc	0	0	0	0	0	
RIDASCREEN	0	0	0	0	0	
OC Sensor	0	0	0	0	0	
OC Pledia	0	0	0	0	0	
TOTAL (after deduplication)	**1**	**0**	**1**	**1**	**0**	**3**

British Society of Gastroenterology Annual Meeting 2011–15

Date searched: 13 April 2016.

Records found: 6.

www.bsg.org.uk/education/meeting/index.html

British Society of Gastroenterology Annual Meeting 2011

www.bsg.org.uk/images/stories/docs/education/2011_bsg_prog_text.pdf

British Society of Gastroenterology Annual Meeting 2012

www.bsg.org.uk/images/stories/docs/education/2012_ddf_prog_text.pdf

British Society of Gastroenterology Annual Meeting 2013

www.bsg.org.uk/images/stories/docs/education/2013_bsg_prog_text.pdf

British Society of Gastroenterology Annual Meeting 2014

www.bsg.org.uk/images/stories/docs/education/2014_bsg_prog_text.pdf

2015 – 2nd Digestive Disorders Federation Conference 22–25 June 2015 – Joint conference with The Association of Coloproctology of Great Britain & Ireland (ACPGBI), Association of Upper Gastrointestinal Surgeons (AUGIS), British Association for Parenteral and Enteral Nutrition (BAPEN), British Association for the Study of the Liver (BASL), British Society of Gastroenterology (BSG)

http://gut.bmj.com/content/64/Suppl_1.toc

Search terms	2011	2012	2013	2014	2015	TOTAL
faecal immunochemical	0	0	1	1	3	
fecal immunochemical	0	0	0	0	0	
faecal immuno-chemical	0	0	0	0	0	
fecal immuno-chemical	0	0	0	0	0	
FIT	0	1	1	0	3	
iFOBT	0	0	0	0	0	
FOB Gold	0	0	0	0	0	
FOBGold	0	0	0	0	0	
JACKarc	0	0	0	0	0	
RIDASCREEN	0	0	0	0	0	
OC Sensor	0	0	0	0	1	
OC Pledia	0	0	0	0	0	
TOTAL (after deduplication)	**0**	**1**	**1**	**1**	**3**	**6**

EuroMedLab: International Federation of Clinical Chemistry and Laboratory Medicine/ European Federation of Clinical Chemistry and Laboratory Medicine, European Congress of Clinical Chemistry and Laboratory Medicine 2011–15 (every 2 years)

Date searched: 13 April 2016.

Records found: 5.

www.ifcc.org/ifcc-congresses-and-conferences/ifcc-eflm-euromedlab-congresses/

EuroMedLab 2011 – 19th IFCC-EFCC European Congress of Clinical Chemistry and Laboratory Medicine

http://ukb.lf1.cuni.cz/abstrakta/ifcc2011_abstr.pdf

EuroMedLab 2013 - 20th IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine

www.sibioc.it/bc/numero/bcnum/132

EuroMedLab 2015 – 21st IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine

www.degruyter.com/view/j/cclm.2015.53.issue-s1/issue-files/cclm.2015.53.issue-s1.xml

Search terms	2011	2013	2015	TOTAL
faecal immunochemical	0	1	1	
fecal immunochemical	0	2	0	
faecal immuno-chemical	0	0	0	
fecal immuno-chemical	0	0	0	
FIT	0	1	1	
iFOBT	0	0	0	
FOB Gold	1	1	0	

Search terms	2011	2013	2015	TOTAL
FOBGold	0	0	0	
JACKarc	0	0	0	
RIDASCREEN	0	0	0	
OC Sensor	0	0	1	
OC Pledia	0	0	0	
TOTAL (after deduplication)	**1**	**2**	**2**	**5**

United European Gastroenterology Week 2011–15

Date searched: 4 May 2016.

Records found: 47.

www.ueg.eu/week/

23rd United European Gastroenterology Week

Barcelona, Spain. October 24–28, 2015

www.ueg.eu/epaper/UEGWeek.2015.FinalProgramme/files/assets/common/downloads/publication.pdf

22nd United European Gastroenterology Week

Vienna, Austria. October 18–22, 2014

www.ueg.eu/fileadmin/user_upload/documents/week14/ueg%20week%202014_final_programme.pdf

21st United European Gastroenterology Week

Berlin, Germany. October 12–16, 2013

www.ueg.eu/fileadmin/user_upload/documents/Week13/ueg_week_2013_final_programme.pdf

20th United European Gastroenterology Week

Amsterdam, the Netherlands. October 20–24, 2012

www.ueg.eu/fileadmin/user_upload/documents/Week13/ueg_week_2012.final_programme.pdf

19th United European Gastroenterology Week 2011

Stockholm, Sweden. October 21–26, 2011

www.hungaronotes.hu/minden/UEGW2011.pdf

Search terms	2011	2012	2013	2014	2015	TOTAL
faecal immunochemical	2	3	1	1	2	
fecal immunochemical	0	6	2	4	6	
faecal immuno-chemical	0	0	0	0	0	
fecal immuno-chemical	0	0	0	0	0	
FIT	6	4	3	2	4	
iFOBT	0	0	1	0	0	
FOB Gold	0	0	0	0	0	
FOBGold	0	0	0	0	0	
JACKarc	0	0	0	0	0	
RIDASCREEN	0	0	0	0	0	
OC Sensor	0	0	0	0	0	
OC Pledia	0	0	0	0	0	
TOTAL (after deduplication)	**8**	**13**	**7**	**7**	**12**	**47**

Cost-effectiveness searches

Economic evaluations and cost studies

MEDLINE (via Ovid): 1946 to March Week 4 2016
Date searched: 4 April 2016.

Records found: 818.

1. exp Colonoscopy/ (23,858)
2. Colonoscop$.ti,ab,ot,hw. (28,519)
3. Coloscop$.ti,ab,ot,hw. (579)
4. Sigmoidoscop$.ti,ab,ot,hw. (6409)
5. or/1-4 (32,887)
6. Colonography, Computed Tomographic/ (1746)
7. virtual colonoscop$.ti,ab,ot,hw. (501)
8. CT colonograph$.ti,ab,ot,hw. (1107)
9. CT pneumocolon.ti,ab,ot,hw. (12)
10. computed tomographic colonograph$.ti,ab,ot,hw. (263)
11. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
12. or/6-11 (2091)
13. Magnetic Resonance Imaging/ (309,510)
14. magnetic resonance imaging.ti,ab,ot,hw. (360,372)
15. (MRI or MRIs or NMRI).ti,ab,ot,hw. (148,957)
16. (magneti?ation transfer adj1 imaging).ti,ab,ot,hw. (413)
17. MR imaging.ti,ab,ot,hw. (32,911)
18. NMR imaging.ti,ab,ot,hw. (1135)
19. magnetic resonance tomography.ti,ab,ot,hw. (1668)
20. MR tomography.ti,ab,ot,hw. (342)
21. chemical shift imaging.ti,ab,ot,hw. (794)
22. proton spin tomography.ti,ab,ot,hw. (34)

23. zeugmatography.ti,ab,ot,hw. (22)
24. or/13-23 (393,772)
25. exp Tomography, X-Ray Computed/ (334,373)
26. (CAT scan$ or CT scan$ or CT x-ray$ or CT xray$).ti,ab,ot,hw. (66,895)
27. (comput$ tomograph$ or computed xray tomograph$ or computed x-ray tomograph$ or computeri?ed axial tomograph$).ti,ab,ot,hw. (196,347)
28. electron beam tomograph$.ti,ab,ot,hw. (375)
29. tomodensitometry.ti,ab,ot,hw. (584)
30. or/25-29 (424,513)
31. 5 or 12 or 24 or 30 (763,480)
32. exp colorectal neoplasms/ (162,710)
33. exp cecal neoplasms/ (4892)
34. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (199,696)
35. CRC.ti,ab,ot. (13,878)
36. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1846)
37. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1676)
38. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (26)
39. or/32-38 (208,381)
40. 31 and 39 (26,596)
41. economics/ (26,664)
42. exp "costs and cost analysis"/ (195,358)
43. economics, dental/ (1876)
44. exp "economics, hospital"/ (21,229)
45. economics, medical/ (8858)
46. economics, nursing/ (3933)
47. economics, pharmaceutical/ (2608)
48. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (471,438)
49. (expenditure$ not energy).ti,ab. (18,999)
50. (value adj1 money).ti,ab. (24)
51. budget$.ti,ab. (18,713)
52. or/41-51 (601,712)
53. ((energy or oxygen) adj cost).ti,ab. (2826)
54. (metabolic adj cost).ti,ab. (868)
55. ((energy or oxygen) adj expenditure).ti,ab. (17,419)
56. or/53-55 (20,370)
57. 52 not 56 (597,185)
58. letter.pt. (876,097)
59. editorial.pt. (373,604)
60. historical article.pt. (328,206)
61. or/58-60 (1,561,761)
62. 57 not 61 (567,144)
63. 40 and 62 (1448)
64. limit 63 to yr = "2005-Current" (818)

Economics terms based on Costs filter:

- Centre for Reviews and Dissemination (CRD). *Search strategies: NHS EED MEDLINE using OvidSP (Economics Filter)*. York: CRD; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp (accessed 2 June 2014).[146]

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via Ovid): 1 April 2016

Date searched: 4 April 2016.

Records found: 103.

1. exp Colonoscopy/ (28)
2. Colonoscop$.ti,ab,ot,hw. (2422)
3. Coloscop$.ti,ab,ot,hw. (7)
4. Sigmoidoscop$.ti,ab,ot,hw. (207)
5. or/1-4 (2536)
6. Colonography, Computed Tomographic/ (0)
7. virtual colonoscop$.ti,ab,ot,hw. (43)
8. CT colonograph$.ti,ab,ot,hw. (94)
9. CT pneumocolon.ti,ab,ot,hw. (0)
10. computed tomographic colonograph$.ti,ab,ot,hw. (26)
11. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
12. or/6-11 (146)
13. Magnetic Resonance Imaging/ (448)
14. magnetic resonance imaging.ti,ab,ot,hw. (18,196)
15. (MRI or MRIs or NMRI).ti,ab,ot,hw. (18,665)
16. (magneti?ation transfer adj1 imaging).ti,ab,ot,hw. (41)
17. MR imaging.ti,ab,ot,hw. (1820)
18. NMR imaging.ti,ab,ot,hw. (73)
19. magnetic resonance tomography.ti,ab,ot,hw. (29)
20. MR tomography.ti,ab,ot,hw. (6)
21. chemical shift imaging.ti,ab,ot,hw. (49)
22. proton spin tomography.ti,ab,ot,hw. (0)
23. zeugmatography.ti,ab,ot,hw. (0)
24. or/13-23 (30,159)
25. exp Tomography, X-Ray Computed/ (392)
26. (CAT scan$ or CT scan$ or CT x-ray$ or CT xray$).ti,ab,ot,hw. (7114)
27. (comput$ tomograph$ or computed xray tomograph$ or computed x-ray tomograph$ or computeri?ed axial tomograph$).ti,ab,ot,hw. (23,966)
28. electron beam tomograph$.ti,ab,ot,hw. (8)
29. tomodensitometry.ti,ab,ot,hw. (14)
30. or/25-29 (28,315)
31. 5 or 12 or 24 or 30 (56,276)
32. exp colorectal neoplasms/ (154)
33. exp cecal neoplasms/ (1)
34. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (14,543)
35. CRC.ti,ab,ot. (2480)
36. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (195)

37. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (38)
38. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (0)
39. or/32-38 (14,877)
40. 31 and 39 (1940)
41. economics/ (3)
42. exp "costs and cost analysis"/ (205)
43. economics, dental/ (0)
44. exp "economics, hospital"/ (19)
45. economics, medical/ (0)
46. economics, nursing/ (0)
47. economics, pharmaceutical/ (0)
48. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (71,397)
49. (expenditure$ not energy).ti,ab. (2126)
50. (value adj1 money).ti,ab. (4)
51. budget$.ti,ab. (2907)
52. or/41-51 (74,321)
53. ((energy or oxygen) adj cost).ti,ab. (377)
54. (metabolic adj cost).ti,ab. (116)
55. ((energy or oxygen) adj expenditure).ti,ab. (1622)
56. or/53-55 (2060)
57. 52 not 56 (73,745)
58. letter.pt. (32,301)
59. editorial.pt. (24,232)
60. historical article.pt. (183)
61. or/58-60 (56,696)
62. 57 not 61 (73,074)
63. 40 and 62 (114)
64. limit 63 to yr="2005 -Current" (103)

Economics terms based on Costs filter:

- Centre for Reviews and Dissemination (CRD). *Search Strategies: NHS EED MEDLINE using OvidSP (Economics Filter)*. York: CRD; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp (accessed 2 June 2014).[146]

EMBASE (via Ovid): 1974 to 1 April 2016

Date searched: 4 April 2016.

Records found: 2333.

1. Colonoscopy/ (54,012)
2. Sigmoidoscopy/ (10,176)
3. Colonoscop$.ti,ab,ot,hw. (61,058)
4. Coloscop$.ti,ab,ot,hw. (987)
5. Sigmoidoscop$.ti,ab,ot,hw. (11,721)
6. or/1-5 (67,824)
7. computed tomographic colonography/ (3341)
8. virtual colonoscop$.ti,ab,ot,hw. (723)
9. CT colonograph$.ti,ab,ot,hw. (1574)
10. CT pneumocolon.ti,ab,ot,hw. (21)

11. computed tomographic colonograph$.ti,ab,ot,hw. (3369)
12. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
13. or/7-12 (3740)
14. nuclear magnetic resonance imaging/ (556,588)
15. Magnetic resonance imaging.ti,ab,ot,hw. (629,542)
16. (MRI or MRIs or NMRI).ti,ab,ot,hw. (272,277)
17. (magneti?ation transfer adj1 imaging).ti,ab,ot,hw. (571)
18. MR imaging.ti,ab,ot,hw. (42,912)
19. NMR imaging.ti,ab,ot,hw. (1406)
20. magnetic resonance tomography.ti,ab,ot,hw. (1496)
21. MR tomography.ti,ab,ot,hw. (344)
22. chemical shift imaging.ti,ab,ot,hw. (982)
23. proton spin tomography.ti,ab,ot,hw. (11)
24. zeugmatography.ti,ab,ot,hw. (26)
25. or/14-24 (662,853)
26. exp computer assisted tomography/ (713,414)
27. (CAT scan$ or CT scan$ or CT x-ray$ or CT xray$).ti,ab,ot,hw. (117,999)
28. (comput$ tomograph$ or computed xray tomograph$ or computed x-ray tomograph$ or computeri?ed axial tomograph$).ti,ab,ot,hw. (351,851)
29. electron beam tomograph$.ti,ab,ot,hw. (2201)
30. tomodensitometry.ti,ab,ot,hw. (716)
31. or/26-30 (771,131)
32. 6 or 13 or 25 or 31 (1,312,128)
33. exp colon tumor/ (240,252)
34. exp rectum tumor/ (182,819)
35. exp colon cancer/ (191,943)
36. exp rectum cancer/ (148,848)
37. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (318,696)
38. CRC.ti,ab,ot. (27,373)
39. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (2651)
40. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1929)
41. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (29)
42. or/33-41 (330,526)
43. 32 and 42 (52,394)
44. health-economics/ (35,302)
45. exp economic-evaluation/ (240,103)
46. exp health-care-cost/ (231,067)
47. exp pharmacoeconomics/ (177,750)
48. or/44-47 (530,895)
49. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (725,833)
50. (expenditure$ not energy).ti,ab. (28,158)
51. (value adj2 money).ti,ab. (1676)
52. budget$.ti,ab. (28,112)
53. or/49-52 (753,216)
54. 48 or 53 (1,043,923)
55. letter.pt. (930,553)

56. editorial.pt. (504,001)
57. note.pt. (634,165)
58. or/55-57 (2,068,719)
59. 54 not 58 (947,501)
60. (metabolic adj cost).ti,ab. (1063)
61. ((energy or oxygen) adj cost).ti,ab. (3494)
62. ((energy or oxygen) adj expenditure).ti,ab. (23,677)
63. or/60-62 (27,341)
64. 59 not 63 (941,755)
65. exp animal/ (21,427,388)
66. exp animal-experiment/ (1,922,177)
67. nonhuman/ (4,721,186)
68. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5,295,240)
69. or/65-68 (23,039,014)
70. exp human/ (16,996,370)
71. exp human-experiment/ (350,705)
72. 70 or 71 (16,997,816)
73. 69 not (69 and 72) (6,042,168)
74. 64 not 73 (867,075)
75. 43 and 74 (3250)
76. **limit 75 to yr = "2005-Current" (2333)**

Economics terms based on Costs filter:

- Centre for Reviews and Dissemination (CRD). *Search Strategies: NHS EED EMBASE using OvidSP (Economics Filter)*. York: CRD; 2014. URL: www.crd.york.ac.uk/crdweb/searchstrategies.asp (accessed 4 April 2016).[146]

NHS Economic Evaluation Database (Wiley) (via the internet): Issue 2 of 4, April 2015

Date searched: 4 April 2016.

Records found: 126.

#1 MeSH descriptor: [Colonoscopy] explode all trees (1772)

#2 Colonoscop* or Coloscop* or Sigmoidoscop* (3631)

#3 #1 or #2 (3631)

#4 MeSH descriptor: [Colonography, Computed Tomographic] explode all trees (128)

#5 "virtual colonoscop*" or "CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon" (200)

#6 #4 or #5 (218)

#7 MeSH descriptor: [Magnetic Resonance Imaging] this term only (5990)

#8 "magnetic resonance imaging" or MRI or MRIs or NMRI (13,927)

#9 "magneti?ation transfer" near/1 imaging (18)

#10 "MR imaging" or "NMR imaging" or "magnetic resonance tomography" or "MR tomography" (854)

#11 "chemical shift imaging" or "proton spin tomography" or zeugmatography (20)

#12 #7 or #8 or #9 or #10 or #11 (14,073)

#13 [mh "Tomography, X-Ray Computed"] (4799)

#14 "CAT scan*" or "CT scan*" or "CT x-ray*" or "CT xray*" (2684)

#15 "comput* tomograph*" or "computed xray tomograph*" or "computed x-ray tomograph*" or "computeri?ed axial tomograph*" (8685)

#16 "electron beam tomograph*" or tomodensitometry (45)

#17 #13 or #14 or #15 or #16 (11,656)

#18 #3 or #6 or #12 or #17 (27,348)

#19 MeSH descriptor: [Colorectal Neoplasms] explode all trees (6056)

#20 MeSH descriptor: [Cecal Neoplasms] explode all trees (9)

#21 (colorect* or rectal* or rectum* or colon* or sigma* or sigmo* or rectosigm* or bowel* or anal or anus) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (12,310)

#22 CRC (1341)

#23 (cecum or cecal or caecum or caecal or ileocecal or ilaeocaecal or ileocecum or ilaeocaecum) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (98)

#24 "large intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (54)

#25 "lower intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

#26 #19 or #20 or #21 or #22 or #23 or #24 or #25 (12,665)

#27 #18 and #26 Publication Year from 2005 to 2016, in Economic Evaluations (126)

EconLit (via EBSCOhost): 2005 to 1 February 2016

Date searched: 5 April 2016.

Records found: 13.

S1 Colonoscop* or Coloscop* or Sigmoidoscop* (24)

S2 "virtual colonoscop*" or "CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon" (4)

S3 "magnetic resonance imaging" or MRI or MRIs or NMRI (115)

S4 "magneti?ation transfer" N1 imaging (0)

S5 "MR imaging" or "NMR imaging" or "magnetic resonance tomography" or "MR tomography" (1)

S6 "chemical shift imaging" or "proton spin tomography" or zeugmatography (0)

S7 "CAT scan*" or "CT scan*" or "CT x-ray*" or "CT xray*" (15)

S8 "comput* tomograph*" or "computed xray tomograph*" or "computed x-ray tomograph*" or "computeri?ed axial tomograph*" (28)

S9 "electron beam tomograph*" or tomodensitometry (0)

S10 S1 OR S2 OR S3 or S4 or S5 or S6 or S7 or S8 or S9 (173)

S11 (colorect* or rectal* or rectum* or colon* or sigma* or sigmo* or rectosigm* or bowel* or anal or anus) N3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (104)

S12 CRC (332)

S13 (cecum or cecal or caecum or caecal or ileocecal or ilaeocaecal or ileocecum or ilaeocaecum) N3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

S14 "large intestin*" N3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

S15 "lower intestin*" N3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

S16 S11 OR S12 OR S13 OR S14 OR S15 (410)

S17 S10 AND S16 (14)

S18 (ZR "2005") or (ZR "2006") or (ZR "2007") or (ZR "2008") or (ZR "2009") or (ZR "2010") or (ZR "2011") or (ZR "2012") or (ZR "2013") or (ZR "2014") or (ZR "2015") or (ZR "2016") (638,824)

S19 S17 AND S18 (13)

Cost-Effectiveness Analysis Registry (via the internet)

https://research.tufts-nemc.org/cear4/Home.aspx

Date searched: 5 April 2016.

Records found: 96.

Search term (basic search)	Records found
colonoscopy	24
Computed tomographic colonography	0
CTC	1
coloscopy	0
sigmoidoscopy	11
magnetic resonance imaging	21
MRI	28
CT scan	11
CAT scan	0
TOTAL	**96**

Research Papers in Economics IDEAS database (via internet)

https://ideas.repec.org/

Date searched: 5 April 2016.

Records found: 21.

(colonoscopy | "computed tomographic colonography" | "CT colonography" | coloscopy | sigmoidoscopy | "magnetic resonance imaging" | MRI | "CT scan" | "CAT scan") + (colorectal | rectal | rectum | colon | bowel | intestine)

Adverse events and mortality data

MEDLINE (via Ovid): 1946 to March Week 4 2016

Date searched: 5 April 2016.

Records found: 759.

1. exp colorectal neoplasms/ (162,710)
2. exp cecal neoplasms/ (4892)
3. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (199,696)
4. CRC.ti,ab,ot. (13,878)
5. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1846)
6. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1676)
7. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (26)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (208,381)
9. exp Colonoscopy/ae, mo [Adverse Effects, Mortality] (1888)

10. Colonography, Computed Tomographic/ae, mo [Adverse Effects, Mortality] (82)
11. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (185)
12. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (39)
13. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (118)
14. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (11)
15. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (4)
16. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (3)
17. or/9-16 (2209)
18. 8 and 17 (762)
19. exp animals/ not (exp animals/ and humans/) (4,208,134)
20. **18 not 19 (759)**

Adverse events filter based on:

- Appendix 4: Searching for adverse events. In Centre for Reviews and Dissemination (CRD). *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care: An Update of CRD's Guidance*. York: University of York; 2009. pp. 253–4.[147]

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via Ovid): 4 April 2016

Date searched: 5 April 2016.

Records found: 20.

1. exp colorectal neoplasms/ (302)
2. exp cecal neoplasms/ (9)
3. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (14,770)
4. CRC.ti,ab,ot. (2502)
5. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (205)
6. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (38)
7. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (0)
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (15,116)
9. exp Colonoscopy/ae, mo [Adverse Effects, Mortality] (2)
10. Colonography, Computed Tomographic/ae, mo [Adverse Effects, Mortality] (0)
11. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (25)

12. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (10)
13. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (12)
14. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (1)
15. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (0)
16. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (0)
17. or/9-16 (47)
18. 8 and 17 (20)
19. exp animals/ not (exp animals/ and humans/) (2786)
20. **20 18 not 19 (20)**

Adverse events filter based on:

- Appendix 4: Searching for adverse events. In *Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care: An Update of CRD's Guidance*. York: University of York; 2009. pp. 253–4.[147]

EMBASE (via Ovid): 1974 to 4 April 2016

Date searched: 5 April 2016.

Records found: 539.

1. exp colon tumor/ (240,283)
2. exp rectum tumor/ (182,837)
3. exp colon cancer/ (191,971)
4. exp rectum cancer/ (148,865)
5. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (31,732)
6. CRC.ti,ab,ot. (27,377)
7. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (2651)
8. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1929)
9. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (29)
10. or/1-9 (330,564)
11. colonoscopy/ae, co [Adverse Drug Reaction] (346)
12. sigmoidoscopy/ae, co [Adverse Drug Reaction, Complication] (70)
13. computed tomographic colonography/ae, co [Adverse Drug Reaction] (10)
14. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (398)
15. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (101)
16. ((colonoscop$ or coloscop$ or sigmoidoscop$) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (224)

17. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (safe or safety or side effect$ or undesirable effect$ or treatment emergent or tolerability)).ti,ab. (14)
18. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab. (5)
19. ((CT colonograph$ or CT pneumocolon or computed tomographic colonograph$ or computed tomographic pneumocolon) adj3 (mortalit$ or dead or death or deaths or died or fatal$)).ti,ab. (3)
20. or/11-19 (1117)
21. 10 and 20 (543)
22. animal/ (1,738,058)
23. animal experiment/ (1,920,454)
24. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6,186,843)
25. or/22-24 (6,186,843)
26. exp human/ (16,998,345)
27. human experiment/ (350,771)
28. or/26-27 (16,999,791)
29. 25 not (25 and 28) (4,867,829)
30. **21 not 29 (539)**

Adverse events filter based on:

- Appendix 4: searching for adverse events. In Centre for Reviews and Dissemination (CRD). *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care: An update of CRD's Guidance*. York: University of York; 2009. pp. 253–4.[147]

Cochrane Central Register of Controlled Trials (Wiley) (via internet): issue 3 of 12, March 2016

Date searched: 5 April 2016.

Records found: 114.

#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees (6056)

#2 MeSH descriptor: [Cecal Neoplasms] explode all trees (9)

#3 (colorect* or rectal* or rectum* or colon* or sigma* or sigmo* or rectosigm* or bowel* or anal or anus) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (12,310)

#4 CRC (1341)

#5 (cecum or cecal or caecum or caecal or ileocecal or ilaeocaecal or ileocecum or ilaeocaecum) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (98)

#6 "large intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (54)

#7 "lower intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 (12,665)

#9 MeSH descriptor: [Colonoscopy] explode all trees and with qualifier(s): [Adverse effects - AE, Mortality - MO] (159)

#10 MeSH descriptor: [Colonography, Computed Tomographic] explode all trees and with qualifier(s): [Adverse effects - AE, Mortality - MO] (6)

#11 (colonoscop* or coloscop* or sigmoidoscop*) near/3 (safe or safety or "side effect*" or "undesirable effect*" or "treatment emergent" or tolerability) (143)

#12 (colonoscop* or coloscop* or sigmoidoscop*) near/3 (adverse near/2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (271)

#13 (colonoscop* or coloscop* or sigmoidoscop*) near/3 (mortalit* or dead or death or deaths or died or fatal*) (55)

#14 ("CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon") near/3 (safe or safety or "side effect*" or "undesirable effect*" or "treatment emergent" or tolerability) (3)

#15 ("CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon") near/3 (adverse near/2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (1)

#16 ("CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon") near/3 (mortalit* or dead or death or deaths or died or fatal*) (3)

#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 (445)

#18 #8 and #17 in Trials (114)

Adverse events filter based on:

- Appendix 4: searching for adverse events. In Centre for Reviews and Dissemination (CRD). *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care: An upDate of CRD's Guidance*. York: University of York; 2009. pp. 253–4.[147]

Utility data

MEDLINE (via Ovid): 1946 to March Week 4 2016

Date searched: 5 April 2016.

Records found: 142.

1. exp Colonoscopy/ (23,858)
2. Colonoscop$.ti,ab,ot,hw. (28,519)
3. Coloscop$.ti,ab,ot,hw. (579)
4. Sigmoidoscop$.ti,ab,ot,hw. (6409)
5. or/1-4 (32,887)
6. Colonography, Computed Tomographic/ (1746)
7. virtual colonoscop$.ti,ab,ot,hw. (501)

8. CT colonograph$.ti,ab,ot,hw. (1107)
9. CT pneumocolon.ti,ab,ot,hw. (12)
10. computed tomographic colonograph$.ti,ab,ot,hw. (263)
11. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
12. or/6-11 (2091)
13. 5 or 12 (33,666)
14. exp colorectal neoplasms/ (162,710)
15. exp cecal neoplasms/ (4892)
16. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (199,696)
17. CRC.ti,ab,ot. (13,878)
18. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1846)
19. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1676)
20. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (26)
21. or/14-20 (208,381)
22. 13 and 21 (17,376)
23. quality-adjusted life years/ or quality of life/ (141,086)
24. (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (16,837)
25. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1063)
26. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (3105)
27. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (486)
28. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (343)
29. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (283)
30. "health related quality of life".ti,ab,ot. (23,887)
31. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (6861)
32. "assessment of quality of life".ti,ab,ot. (1231)
33. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (4671)
34. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (11,290)
35. (hye or hyes).ti,ab,ot. (54)
36. health$ year$ equivalent$.ti,ab,ot. (38)
37. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (947)
38. (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (630)
39. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (1999)
40. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (7724)
41. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (4122)
42. 15d.ti,ab,ot. (1230)

43. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (247)
44. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (7273)
45. (utilities or disutili$).ti,ab,ot. (4335)
46. (Functional Assessment of Cancer Therapy$ or FACT-G).ti,ab,ot. (1334)
47. (QLQ-C30 or QLQ-C-30 or EORTC QLQ$ or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or "EORTC Quality of Life Questionnaire").ti,ab,ot. (2735)
48. or/23-47 (167,380)
49. 22 and 48 (142)
50. animals/ not (animals/ and humans/) (4,175,932)
51. **49 not 50 (142)**

Health-related quality of life (HRQoL) free-text terms based on:

- Figure 4: Common free-text terms for electronic database searching for HSUVs. In Papaioannou D, Brazier JE, Paisley S. *NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the Literature*. 2011. URL: www.nicedsu.org.uk (accessed 18 August 2011).[147]

MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily Update (via Ovid): 4 April 2016

Date searched: 5 April 2016.

Records found: 15.

1. exp Colonoscopy/ (37)
2. Colonoscop$.ti,ab,ot,hw. (2467)
3. Coloscop$.ti,ab,ot,hw. (7)
4. Sigmoidoscop$.ti,ab,ot,hw. (208)
5. or/1-4 (2581)
6. Colonography, Computed Tomographic/ (1)
7. virtual colonoscop$.ti,ab,ot,hw. (43)
8. CT colonograph$.ti,ab,ot,hw. (95)
9. CT pneumocolon.ti,ab,ot,hw. (0)
10. computed tomographic colonograph$.ti,ab,ot,hw. (26)
11. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
12. or/6-11 (147)
13. 5 or 12 (2635)
14. exp colorectal neoplasms/ (302)
15. exp cecal neoplasms/ (9)
16. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (14,770)
17. CRC.ti,ab,ot. (2502)
18. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (205)
19. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (38)
20. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (0)
21. or/14-20 (15,116)
22. 13 and 21 (1285)

23. quality-adjusted life years/ or quality of life/ (344)
24. (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (1882)
25. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (480)
26. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (462)
27. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (68)
28. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (14)
29. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (48)
30. "health related quality of life".ti,ab,ot. (3528)
31. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (999)
32. "assessment of quality of life".ti,ab,ot. (123)
33. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (882)
34. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (1608)
35. (hye or hyes).ti,ab,ot. (3)
36. health$ year$ equivalent$.ti,ab,ot. (2)
37. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (136)
38. (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (58)
39. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (336)
40. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (1165)
41. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (628)
42. 15d.ti,ab,ot. (118)
43. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (32)
44. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (951)
45. (utilities or disutili$).ti,ab,ot. (652)
46. (Functional Assessment of Cancer Therapy$ or FACT-G).ti,ab,ot. (168)
47. (QLQ-C30 or QLQ-C-30 or EORTC QLQ$ or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or "EORTC Quality of Life Questionnaire").ti,ab,ot. (372)
48. or/23-47 (9820)
49. 22 and 48 (12)
50. animals/ not (animals/ and humans/) (2780)
51. **49 not 50 (12)**

HRQoL free-text terms based on:

- Figure 4: Common free-text terms for electronic database searching for HSUVs. In Papaioannou D, Brazier JE, Paisley S. *NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the Literature*. 2011. URL: www.nicedsu.org.uk (accessed 18 August 2011).[148]

EMBASE (via Ovid): 1974 to 4 April 2016

Date searched: 5 April 2016.

Records found: 208.

1. Colonoscopy/ (54,017)
2. Sigmoidoscopy/ (10,176)
3. Colonoscop$.ti,ab,ot,hw. (61,064)
4. Coloscop$.ti,ab,ot,hw. (987)
5. Sigmoidoscop$.ti,ab,ot,hw. (11,721)
6. or/1-5 (67,830)
7. computed tomographic colonography/ (3342)
8. virtual colonoscop$.ti,ab,ot,hw. (723)
9. CT colonograph$.ti,ab,ot,hw. (1574)
10. CT pneumocolon.ti,ab,ot,hw. (21)
11. computed tomographic colonograph$.ti,ab,ot,hw. (3370)
12. computed tomographic pneumocolon.ti,ab,ot,hw. (0)
13. or/7-12 (3741)
14. 6 or 13 (69,101)
15. exp colon tumor/ (240,283)
16. exp rectum tumor/ (182,837)
17. exp colon cancer/ (191,971)
18. exp rectum cancer/ (148,865)
19. ((colorect$ or rectal$ or rectum$ or colon$ or sigma$ or sigmo$ or rectosigm$ or bowel$ or anal or anus) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot,hw. (318,732)
20. CRC.ti,ab,ot. (27,377)
21. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (2651)
22. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (1929)
23. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$)).ti,ab,ot. (29)
24. or/15-23 (330,564)
25. 14 and 24 (33,692)
26. quality adjusted life year/ or quality of life index/ (17,805)
27. Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (18,197)
28. "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (2090)
29. (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (28,658)
30. (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1719)
31. (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (5712)
32. (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (945)
33. (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (373)
34. (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (539)

35. "health related quality of life".ti,ab,ot. (37,958)
36. (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (11,553)
37. "assessment of quality of life".ti,ab,ot. (2056)
38. (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (10,075)
39. (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (19,883)
40. (hye or hyes).ti,ab,ot. (100)
41. health$ year$ equivalent$.ti,ab,ot. (40)
42. (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2395)
43. (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (886)
44. (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (2768)
45. (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (14,817)
46. (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (6976)
47. 15d.ti,ab,ot. (1920)
48. (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (377)
49. (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (12,545)
50. (utilities or disutili$).ti,ab,ot. (7816)
51. (Functional Assessment of Cancer Therapy$ or FACT-G).ti,ab,ot. (2475)
52. (QLQ-C30 or QLQ-C-30 or EORTC QLQ$ or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or "EORTC Quality of Life Questionnaire").ti,ab,ot. (5757)
53. or/26-52 (124,961)
54. 25 and 53 (208)
55. animal/ (1,738,058)
56. animal experiment/ (1,920,454)
57. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6,186,843)
58. or/55-57 (6,186,843)
59. exp human/ (16,998,345)
60. human experiment/ (350,771)
61. or/59-60 (16,999,791)
62. 58 not (58 and 61) (4,867,829)
63. 54 not 62 (208)

HRQoL free-text terms based on:

- Figure 4: Common free-text terms for electronic database searching for HSUVs. In Papaioannou D, Brazier JE, Paisley S. *NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the Literature*. 2011. URL: www.nicedsu.org.uk (accessed 18 August 2011).[148]

NHS Economic Evaluation Database (Wiley) (via the internet): Issue 2 of 4, April 2015; Cochrane Central Register of Controlled Trials (Wiley) (via the internet): Issue 3 of 12, March 2016

Date searched: 6 April 2016.

Records found: NHS EED 84, CENTRAL 22.

#1 MeSH descriptor: [Colonoscopy] explode all trees (1772)

#2 Colonoscop* or Coloscop* or Sigmoidoscop* (3631)

#3 #1 or #2 (3631)

#4 MeSH descriptor: [Colonography, Computed Tomographic] explode all trees (128)

#5 "virtual colonoscop*" or "CT colonograph*" or "CT pneumocolon" or "computed tomographic colonograph*" or "computed tomographic pneumocolon" (200)

#6 #4 or #5 (218)

#7 #3 or #6 (3684)

#8 MeSH descriptor: [Colorectal Neoplasms] explode all trees (6056)

#9 MeSH descriptor: [Cecal Neoplasms] explode all trees (9)

#10 (colorect* or rectal* or rectum* or colon* or sigma* or sigmo* or rectosigm* or bowel* or anal or anus) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (12,310)

#11 CRC (1341)

#12 (cecum or cecal or caecum or caecal or ileocecal or ilaeocaecal or ileocecum or ilaeocaecum) near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (98)

#13 "large intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (54)

#14 "lower intestin*" near/3 (cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) (0)

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14 (12,665)

#16 #7 and #15 (1672)

#17 MeSH descriptor: [Quality-Adjusted Life Years] this term only (4067)

#18 MeSH descriptor: [Quality of Life] this term only (17,726)

#19 sf36 or "sf 36" or "sf-36" or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six" (6863)

#20 sf6 or "sf 6" or "sf-6" or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six" (154)

#21 sf12 or "sf 12" or "sf-12" or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve" (1132)

#22 sf6D or "sf 6D" or "sf-6D" or "short form 6D" or "shortform 6D" or "sf six D" or sfsixD or "shortform six D" or "short form six D" (206)

#23 sf20 or "sf 20" or "sf-20" or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty" (78)

#24 sf8 or "sf 8" or "sf-8" or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight" (66)

#25 "health related quality of life" (7949)

#26 "Quality adjusted life" or "Quality-adjusted-life" (6898)

#27 "assessment of quality of life" (348)

#28 euroqol or "euro qol" or eq5d or "eq 5d" (3194)

#29 hql or hrql or hqol or "h qol" or hrqol or "hr qol" (3007)

#30 hye or hyes (58)

#31 "health* year* equivalent*" (5)

#32 hui or hui1 or hui2 or hui3 or hui4 or "hui-4" or "hui-1" or "hui-2" or "hui-3" (2929)

#33 "quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" (238)

#34 "Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" (370)

#35 QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL* (5551)

#36 timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" (2030)

#37 15d (116)

#38 HSUV* or "health state* value*" or "health state* preference*" or HSPV* (89)

#39 utilit* near/3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*) (4790)

#40 utilities or disutili* (1711)

#41 "Functional Assessment of Cancer Therapy*" or "FACT-G" (588)

#42 "QLQ-C30" or "QLQ-C-30" or "EORTC QLQ*" or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" or "EORTC Quality of Life Questionnaire" (1174)

#43 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 (39,531)

#44 #16 and #43 in Trials and Economic Evaluations (106)

HRQoL free-text terms based on:

- Figure 4: Common free-text terms for electronic database searching for HSUVs. In Papaioannou D, Brazier JE, Paisley S. *NICE DSU Technical Support Document 9: The Identification, Review and Synthesis of Health State Utility Values from the literaTure.* 2011. URL: www.nicedsu.org.uk (accessed 18 August 2011).[147]

School of Health and Related Research Health Utilities Database (via the internet)

www.scharrhud.org/

Date searched: 6 April 2016.

Records found: 10.

colorectal or rectal or rectum or colon or bowel or intestine [Any field]

and

cancer or neoplasm or neoplasms or tumor or tumour [Any field].

Appendix 2 Data extraction tables

TABLE 65 Baseline study details

Study Details	Selection criteria	Participant details	Test manufacturer
Auge 2016[57] **Related publications:** Auge 2014;[66] Auge 2015[72] **Country:** Spain **Funding:** Menarini Diagnósticos, S.A., provided instruments, reagents and technical support **Recruitment:** December 2013 to March 2014 **Study design:** Diagnostic cohort	• Inclusion criteria: Adult patients, attending a hospital outpatient clinic for the investigation of lower abdominal symptoms or polyp surveillance • Exclusion criteria: Patients undergoing CRC screening; history of GI bleeding; active rectal bleeding; menstruation; haematuria; known ulcerative colitis • Study setting: Outpatient clinic • Point in care pathway at which the test is given: Testing was requested in a secondary care outpatient clinic	• Total no. tested: 208 • Median age (range): 63 (22–86) years • Male (%): 44.2 • Altered bowel habit (%): NR • Rectal bleeding (%): NR • Diarrhoea (%): NR • Abdominal pain (%): NR • Anaemia (unspecified) (%): NR • Weight loss (%): NR • Palpable mass (%): NR • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR • SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	Kyowa Medex, Japan
Cubiella 2014 (COLONPREDICT)[55] **Related publications:** Diaz Ondina 2014;[61] Cubiella 2015[73] **Country:** Spain **Funding:** Instituto de Salud Carlos III, Madrid, Spain (PI11/00094) **Recruitment:** April 2012 to November 2012 **Study design:** Diagnostic cohort	• Inclusion criteria: Adult outpatients, with GI symptoms, referred from primary and secondary health care • Exclusion criteria: Pregnancy; undergoing colonoscopy for surveillance following previous history of colonic disease; requiring hospital admission; symptoms had ceased within 3 months before the evaluation • Study setting: Mixed • Point in care pathway at which the test is given: Testing was requested after referral to the gastroenterology outpatient clinic and before colonoscopy • Comments: Data were also presented for the diagnostic performance of individual signs and symptoms and for NICE and SIGN referral criteria. Patients were recruited from primary care and outpatient settings	• Total no. tested: 787 (completed protocol) • Median age (range): 67 (22–91) years • Male (%): 51.1 • Altered bowel habit (%): 56.2 • Rectal bleeding (%): 64 • Diarrhoea (%): NR • Abdominal pain (%): 44.5 • Anaemia (unspecified) (%): NR • Weight loss (%): 21.2 • Palpable mass (%): 2.3 • Constipation (%): 29.2 • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): 38.1 • SIGN criteria for urgent referral (%): 60.4 • Clinical suspicion of CRC (%): NR	Eiken Chemical Co., Tokyo, Japan
Godber 2016[56] **Related publications:** Macdonald 2015;[71] Godber 2014[65] **Country:** Scotland	• Inclusion criteria: Patients (age > 16 years) who had been referred from primary care for endoscopic examination of the lower GI tract. Most common reasons for referral included altered bowel habit, constipation or diarrhoea, abdominal pain,	• Total no. tested: 507 [tested for faecal immunochemical testing and colonoscopy attempted (484 analysed)] • Median age (range): 59 (16–89) years • Male (%): 42.6	Kyowa Medex, Japan

continued

TABLE 65 Baseline study details (*continued*)

Study Details	Selection criteria	Participant details	Test manufacturer
Funding: NHS Lanarkshire; analyser, training and consumables were supplied by Kyowa Medex Co., Ltd, Tokyo, Japan **Recruitment:** June 2013 to December 2013 **Study design:** Diagnostic cohort	fresh rectal bleeding, follow-up of previous disease, anaemia, weight loss and abnormal CT findings • Exclusion criteria: Referred for investigation of a positive test result from the Scottish Bowel Screening Programme • Study setting: Outpatient clinic • Point in care pathway at which the test is given: Testing was requested after referral for endoscopy	• Altered bowel habit (%): 37.9 • Rectal bleeding (%): 15.2 • Diarrhoea (%): NR • Abdominal pain (%): 17.9 • Anaemia (unspecified) (%): 4.5 • Weight loss (%): 1.6 • Palpable mass (%): NR • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR • SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	
(Confidential information has been removed)	(Confidential information has been removed)	• (Confidential information has been removed)	(Confidential information has been removed)
Krivec 2011[54] **Related publications:** None **Country:** Slovenia **Funding:** NR **Recruitment:** NR to NR **Study design:** Diagnostic cohort	• Inclusion criteria: Adult symptomatic patients, undergoing endoscopic and/or histological examinations • Exclusion criteria: NR • Study setting: Unclear • Point in care pathway at which the test is given: Unclear (patients scheduled for endoscopy) • Comments: Abstract only	• Median age (range): NR • Male (%): NR • Altered bowel habit (%): NR • Rectal bleeding (%): NR • Diarrhoea (%): NR • Abdominal pain (%): NR • Anaemia (unspecified) (%): NR • Weight loss (%): NR • Palpable mass (%): NR • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR • SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	Sentinel Diagnostics
McDonald 2012[13] **Related publications:** None **Country:** Scotland **Funding:** Chief Scientist Office; analyser, training and consumables supplied by Mast Diagnostics Division **Recruitment:** February 2010 to March 2012 **Study design:** Diagnostic cohort	• Inclusion criteria: Patients (age > 16 years) who had been referred from primary care for endoscopic examination of the lower GI tract. Reasons for referral included rectal bleeding, change in bowel habit, iron-deficiency anaemia, abdominal pain, bloating, polyp/CRC surveillance, family history and assessment of IBD • Exclusion criteria: Referred for investigation of a positive test result from the Scottish Bowel Screening Programme • Study setting: Outpatient clinic • Point in care pathway at which the test is given: Testing was requested after referral for endoscopy	• Total no. tested: 280 (completed FIT and endoscopy) • Age range: 16–89 years, for all included participants • Male (%): 40.4 • Altered bowel habit (%): NR • Rectal bleeding (%): NR • Diarrhoea (%): NR • Abdominal pain (%): NR • Anaemia (unspecified) (%): NR • Weight loss (%): NR • Palpable mass (%): NR • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR	Eiken Chemical Co., Tokyo, Japan

TABLE 65 Baseline study details (*continued*)

Study Details	Selection criteria	Participant details	Test manufacturer
		• SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	
Mowat 2015[52] **Related publications:** Steele 2014[74] **Country:** Scotland **Funding:** Detect cancer early, Scottish Government **Recruitment:** October 2013 to March 2014 **Study design:** Diagnostic cohort	• Inclusion criteria: All adult patients referred for investigation of bowel symptoms for any of the following reasons: rectal bleeding, anaemia, diarrhoea, altered bowel habit, abdominal pain and weight loss • Exclusion criteria: NR • Study setting: Primary care • Point in care pathway at which the test is given: Testing was ordered by GPs at the point of referring patients to secondary care • Comments: Data were also presented for the diagnostic performance of individual signs and symptoms, and for the most common findings at colonoscopy	• Total no. tested: 755 (completed FIT and endoscopy) • Median age (range): 64 (16–90) years • Male (%): NR • Altered bowel habit (%): 42.8 • Rectal bleeding (%): 34.2 • Diarrhoea (%): 16.8 • Abdominal pain (%): 11 • Anaemia (unspecified) (%): 6 • Weight loss (%): 0.9 • Palpable mass (%): 0.3 • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR • SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	Eiken Chemical Co., Tokyo, Japan
Rodríguez-Alonso 2015[53] **Related publications:** None **Country:** Spain **Funding:** Societat Catalana de Digestologia, Catalonia, Spain; Instituto de Salud Carlos III; FIS grants **Recruitment:** September 2011 to October 2012 **Study design:** Diagnostic cohort	• Inclusion criteria: Adult patients (age > 18 years) referred for diagnostic colonoscopy; referrals were from GPs, community gastroenterologists and hospital environments • Exclusion criteria: Adenoma surveillance; CRC surveillance; hospitalised patients; previous colectomy; IBD; polyp syndromes • Study setting: Mixed • Point in care pathway at which the test is given: Testing was requested by the GP or at the time of the initial secondary care consultation • Comments: Data were also presented for the diagnostic performance of individual signs and symptoms and for NICE and SIGN referral criteria, and for findings at colonoscopy	• Total no. tested: 1003 (completed FIT and endoscopy) • Median age (range): NR • Male (%): 46.8 • Altered bowel habit (%): NR • Rectal bleeding (%): 34.2 • Diarrhoea (%): 23.5 • Abdominal pain (%): 35.4 • Anaemia (unspecified) (%): NR • Weight loss (%): 19 • Palpable mass (%): NR • Constipation (%): 12.1 • Anaemia (iron deficiency) (%): 18.8 • NICE criteria for urgent referral (%): 29.5 • SIGN criteria for urgent referral (%): 31.2 • Clinical suspicion of CRC (%): NR	Eiken Chemical Co., Tokyo, Japan
Terhaar sive Droste 2011[58] **Related publications:** Oort 2011;[63,69] van Turenhout 2014;[59] van Turenhout 2012;[62] van Turenhout 2011;[68] Oort 2010;[64] van Turenhout 2012;[60] Larbi 2012;[67] van Turenhout 2010[70]	• Inclusion criteria: Adult patients referred for colonoscopy • Exclusion criteria: No informed consent; hemicolectomy; IBD; age < 18 years • Study setting: Outpatient clinic • Point in care pathway at which the test is given: Patients scheduled for colonoscopy were requested to perform a FIT before	• Total no. tested: (confidential information has been removed) • Clinical suspicion of CRC (%): 2.8 • Comments: Some patients had multiple symptoms; patients were assigned to a symptom group based on the most severe symptom experienced, that is, in order	

continued

TABLE 65 Baseline study details (*continued*)

Study Details	Selection criteria	Participant details	Test manufacturer
Country: The Netherlands **Funding:** Nycomed BV; Hoofddorp to 'the Amsterdam Gutclub'; the OC-Sensor MICRO desktop analyser was provided by Eiken Chemical Co., Tokyo, Japan **Recruitment:** May 2006 to May 2010 **Study design:** Diagnostic cohort	bowel preparation for colonoscopy • Comments: Data for the symptomatic subgroup were provided, in confidence, by the authors (Sietze van Turenhout, personal communication)	of rectal bleeding, anaemia, clinical suspicion of CRC, change in bowel habit	
Thomas 2016[75] **Related publications:** None **Country:** England **Funding:** Reagents and FIT devices provided by industry **Recruitment:** March 2015 to March 2016 **Study design:** Diagnostic cohort	• Inclusion criteria: Adult symptomatic patients, recruited after their first 2-week wait clinic at University Hospitals Coventry and Warwickshire NHS Trust, UK • Exclusion criteria: NR • Study setting: Outpatient clinic • Point in care pathway at which the test is given: Testing was requested in secondary care. Patients were recruited after their first 2-week wait clinic • Comments: Abstract only	• Total no. tested: 450 • Median age (range): 67 (29–93) years • Male (%): NR • Altered bowel habit (%): NR • Rectal bleeding (%): NR • Diarrhoea (%): NR • Abdominal pain (%): NR • Anaemia (unspecified) (%): NR • Weight loss (%): NR • Palpable mass (%): NR • Constipation (%): NR • Anaemia (iron deficiency) (%): NR • NICE criteria for urgent referral (%): NR • SIGN criteria for urgent referral (%): NR • Clinical suspicion of CRC (%): NR	Kyowa Medex, Tokyo, Japan

NR, not reported.

TABLE 66 Index test and reference standard details

	Index test details				Reference standard details	
Study details	Test analyser	Thresholds (µg Hb/g faeces)	Target conditions	Sample collection, storage and processing	Reference standard details and information recorder	Definition of the target condition
Auge 2016[57]	• HM-JACKarc, Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan • HM-JACKarc automated immunoturbidimetric analyser	> 0, ≥ 10, ≥ 20, ≥ 30, ≥ 40	• Advanced neoplasia	• Patients were asked to collect two consecutive bowel motions, using sample collection devices provided (Kyowa Medex Co., Ltd, Tokyo, Japan) • Participants were asked to store samples at 4 °C and return them to the laboratory with 5 days. Samples were stored at 4 °C and allowed to return to room temperature before analysis within 24 hours • All analyses were carried out by one laboratory technician. The laboratory has a certified total quality management system and the analyser was calibrated every 2 weeks	• Colonoscopy • Colonoscopy was carried out up to the caecum or obstructing carcinoma, if present. The histology of all detected lesions was evaluated by expert pathologists • All lesions were categorised and, if polyps were detected, the polyp site was recorded and polypectomy performed wherever possible	• CRC or HRA (defined as lesions ≥ 1 cm or with a villous component or high-grade dysplasia, or three or more non-advanced adenomas
Cubiella 2014 (COLONPREDICT)[55]	• OC-Sensor; Automated OC-Sensor analyser	≥ 20	• CRC • Advanced neoplasia • CRC location • CRC stage	• No diet or medication restrictions. Participants were instructed to collect from a single faecal sample in which no blood was visible • No further details were reported	• Colonoscopy • Colonoscopy was carried out by experienced endoscopists who performed more than 200 examinations per year. A biopsy was taken when appropriate. Colonoscopy was considered complete if caecal intubation was achieved, unless a complete neoplastic stenosis was found • Information recorded included the location (rectum, colon or proximal to the splenic flexure) and AJCC stage of any CRC; HRA (adenomas measuring ≥ 10 mm, with villous architecture and/or high-grade dysplasia)	• Any CRC • Advanced neoplasia (CRC or HRA) • CRC (located in the rectum); CRC (located in the distal colon); CRC (located in the proximal colon) • CRC (AJCC stage 0); CRC (AJCC stage I); CRC (AJCC stage II); CRC (AJCC stage III); CRC (AJCC stage IV)

continued

TABLE 66 Index test and reference standard details (*continued*)

	Index test details				Reference standard details	
Study details	Test analyser	Thresholds (µg Hb/g faeces)	Target conditions	Sample collection, storage and processing	Reference standard details and information recorder	Definition of the target condition
Godber 2016[56]	• HM-JACKarc • HM-JACKarc automated immunoturbidimetric analyser	≥ 10, ≥ 15, ≥ 20, ≥ 25, ≥ 30, ≥ 35, ≥ 40	• CRC • Advanced neoplasia • All neoplasia • Significant bowel disease	• A single sample collection device (Kyowa Medex Co., Ltd, Tokyo, Japan) was used by the patient, dated and posted back to Department of Biochemistry, Monklands Hospital, Airdrie, Scotland • Stored at 4 °C on arrival until analysis. The mean elapsed time between sampling and receipt was 2.0 days, which is within the manufacturer's documented stability (stable for 120 days at 4 °C and 14 days at 25 °C). All analyses were carried out within 1 week of receipt in the laboratory • All analyses were carried out by a single registered clinical scientist. The laboratory has a certified total quality management system and the analyser was calibrated once per week	• Colonoscopy • Colonoscopy was performed by the endoscopy service at Wishaw General Hospital, which participates in the accreditation scheme of the Joint Accreditation Group on GI Endoscopy • Data were collected on the quality of the investigation (quality of preparation, completeness) and on the results, including number, size and localisation of CRCs, high- and intermediate-risk adenoma (HRA), IBD, colitis, LRA and other colorectal findings. and whether biopsy was performed. Pathological data were collected on all excised and biopsy specimens including polyp type, presence or absence of malignancy, stage of any cancer	• Any CRC • Advanced neoplasia (CRC or HRA); HRA was defined as three or more adenomas, or any adenoma with a diameter ≥ 10 mm • All neoplasia (cancer, or HRA or LRA • Significant bowel disease (cancer, or HRA, or LRA or IBD)
Hospital Clinic de Barcelona 2015	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Krivec 2011[54]	• FOB Gold system, Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy • Modular Roche biochemical analyser	≥ 9	• Significant bowel disease	• No details reported	• Colonoscopy • No details reported	• Malignant disease, polyps or observed bleeding during endoscopy

Study details	Index test details: Test analyser	Index test details: Thresholds (µg Hb/g faeces)	Index test details: Target conditions	Index test details: Sample collection, storage and processing	Reference standard details: Reference standard details and information recorder	Reference standard details: Definition of the target condition
McDonald 2012[13]	• OC-Sensor • OC-Sensor Diana automated immunoturbidimetric analysers, Eiken Chemical Co., Tokyo, Japan	≥ 10	• CRC • Advanced neoplasia • All neoplasia • Significant bowel disease	• Eiken specimen collection device. Patients were instructed to collect and date samples from a single faeces, and to post the sample back to the Scottish Bowel Screening Centre Laboratory immediately • No details about sample storage were reported • All analyses were carried out in the Scottish Bowel Screening Centre Laboratory, by staff whose main role was to perform faecal analyses. The laboratory has a certified total quality management system based on the UK Clinical Pathology Accreditation standard and analysers were calibrated once per month	• Colonoscopy and flexible sigmoidoscopy • Colonoscopy was performed in the Endoscopy Unit • Data were collected on the quality of the investigation (quality of preparation, completeness) and on the results including number, size and localisation of CRCs, HRA and LRA, and whether biopsy was performed. Full pathological data were collected on all excised and biopsy specimens including polyp type, presence or absence of malignancy, stage of any cancer and the characteristics of all adenomas	• Any CRC • Advanced neoplasia (CRC or HRA); HRA was defined as three or more adenomas, or any adenoma with a diameter ≥ 10 mm • All neoplasia (CRC, HRA or LRA) • Significant bowel disease (cancer, or HRA, or LRA or IBD)
Mowat 2015[52]	• OC-Sensor • Io Analyser, Eiken Chemical Co., Tokyo, Japan	≥ 10, ≥ 0	• CRC • Advanced neoplasia • HRA • Significant bowel disease • IBD	• EIKEN specimen collection device. Patients were instructed to collect samples from a single faeces and to return immediately to the GP surgery • The samples were returned at room temperature via the GP surgery and then stored at 4 °C or –20 °C prior to analysis • The laboratory has a total quality management system in place and is accredited to ISO 15189-based standards	• Colonoscopy • Colonoscopy was conducted in accredited endoscopy units and reported by the endoscopist. Diagnoses were confirmed following assessment by a GI pathologist	• Any CRC • Advanced neoplasia (CRC or HRA); HRA was defined as three or more adenomas or any adenoma ≥ 10 mm • Significant bowel disease (CRC, HRA or IBD)

continued

TABLE 66 Index test and reference standard details (*continued*)

	Index test details				Reference standard details	
Study details	Test analyser	Thresholds (µg Hb/g faeces)	Target conditions	Sample collection, storage and processing	Reference standard details and information recorder	Definition of the target condition
Rodríguez-Alonso 2015[53]	• OC-Sensor • MICRO desktop analyser (Eiken)	≥ 20, ≥ 15, ≥ 10, ≥ 0	• CRC • Advanced neoplasia	• Eiken specimen collection device • Patients were instructed to store the sample in the refrigerator at < 4 °C and submit it within 7 days. No details of transportation or laboratory storage conditions were reported • No further details were reported	• Colonoscopy • Colonoscopy was conducted by experienced endoscopists with the patient under conscious sedation. The colonoscopy was considered complete if caecal intubation was achieved, as demonstrated by visualisation of the ileocaecal valve or the appendiceal orifice • The number, size and histology of polyps, and presence or absence of CRC, were recorded	• Any CRC • Advanced neoplasia (CRC or HRA)
Terhaar sive Droste 2011[58]	• OC-Sensor • MICRO desktop analyser (Eiken)	≥ 10, ≥ 15, ≥ 20, ≥ 30, ≥ 40	• CRC • HRA	• Patients were asked to collect a faecal sample the day before colonoscopy and before bowel preparation had started. Illustrated guidance was provided on how to collect a sample without exposure to water or urine. No dietary or medication restrictions were required • Samples were submitted on the day of colonoscopy, stored at –5 °C and analysed within 1 week of collection • Samples were analysed by two experienced technicians	• Colonoscopy • Colonoscopy was conducted in accredited endoscopy units and reported by the endoscopist. Diagnoses were confirmed following assessment by a GI pathologist. A complete colonoscopy was defined as intubation of the caecum with identification of the ileocaecal valve or appendiceal orifice, or intubation up to an obstructing neoplasm	• Any CRC • HRA was defined as > 9 mm, high-grade dysplasia and/or villous adenoma
Thomas 2016[75]	• HM-JACKarc • HM-JACKarc automated immunoturbidimetric analyser	≥ 7	• CRC • Significant bowel disease	• No details reported	• CT/colonoscopy • No further details reported	• Significant bowel disease (CRC, HRA or IBD)

ISO, International Organization for Standardization; LRA, low-risk adenoma.

Appendix 3 Assessments of study quality

A. QUADAS-2 assessments

Auge 2016[57]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive patients, requiring colonoscopy for lower abdominal symptoms or polyp surveillance	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Patients referred for colonoscopy, some polyp surveillance patients included, symptoms not specified	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected two consecutive faecal samples, which were stored at 4 °C until analysis. Faecal immunochemical testing was conducted before colonoscopy	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Colonoscopy was performed blind to the results of the symptoms questionnaire and faecal immunochemical testing	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
All participants appeared to have been included in the analysis. Colonoscopy was conducted 5 days after the index test	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	**RISK: Low**

Cubiella 2014 (COLONPREDICT)[55]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Consecutive patients, with GI symptoms, referred from primary and secondary health care	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Patients referred from a mixture of primary and secondary care. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding)	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
No details of sample collection and storage. Faecal immunochemical testing was performed the week before colonoscopy	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Colonoscopy was performed blind to the results of the symptoms questionnaire and faecal immunochemical testing	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Faecal immunochemical testing was performed 1 week before colonoscopy; 26 patients who did not return a faecal sample and 12 who did not attend for colonoscopy were excluded from the study	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Godber 2016[56]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Patients who had been referred from primary care for endoscopic examination of the lower GI tract	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Patients who were referred for colonoscopy for reasons, which include the following: altered bowel habit, constipation or diarrhoea, abdominal pain, fresh rectal bleeding, follow-up of previous disease, anaemia, weight loss and abnormal CT findings	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected single faecal samples and returned by post. Sample stored at 4 °C. Samples were analysed using a HM-JACKarc automated immunoturbidimetric analyser. The index test was conducted before colonoscopy. ROC analysis was reported, but data were extracted for a range of specified thresholds	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Colonoscopy was performed by the endoscopy service	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
The time interval between index test and reference standard was not reported; 402 people declined to participate, 23 (4.5%) failed colonoscopy	
Was there an appropriate time interval between the index test and reference standard?	Unclear
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Hospital Clinic de Barcelona 2015

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
(Confidential information has been removed)	
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
Could the selection of patients have introduced bias?	(Confidential information has been removed)
B. APPLICABILITY	
(Confidential information has been removed)	
Do the included patients match the question?	(Confidential information has been removed)

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
(Confidential information has been removed)	
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
Could the conduct or interpretation of the index test have introduced bias?	(Confidential information has been removed)
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	(Confidential information has been removed)

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
(Confidential information has been removed)	
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
Could the reference standard, its conduct or its interpretation have introduced bias?	(Confidential information has been removed)
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	(Confidential information has been removed)

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
(Confidential information has been removed)	
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
(Confidential information has been removed)	(Confidential information has been removed)
Could the patient flow have introduced bias?	(Confidential information has been removed)

Krivec 2011[54]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Symptomatic patients undergoing endoscopic and/or histological examinations	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Symptomatic adults undergoing endoscopy and/or histology, patients already referred and symptoms not specified	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
No details of sample collection or storage/processing were reported. The FIT cut-off point was derived from ROC analysis	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it prespecified?	No
Could the conduct or interpretation of the index test have introduced bias?	**RISK: High**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Endoscopy and/or histological examination	
Is the reference standard likely to correctly classify the target condition?	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: High**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
The time interval between index test and reference standard was not reported. No exclusions were reported	
Was there an appropriate time interval between the index test and reference standard?	Unclear
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	unclear
Were all patients included in the analysis?	Unclear
Could the patient flow have introduced bias?	**RISK: Unclear**

McDonald 2012[13]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Patients who had been referred from primary care for endoscopic examination of the lower GI tract	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Patients who were referred for colonoscopy for the following reasons: rectal bleeding, change in bowel habit, iron-deficiency anaemia, abdominal pain, bloating, polyp/CRC surveillance, family history and assessment of IBD	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected single faecal samples and returned by post. No details of sample storage. Samples were analysed using a OC-Sensor. The index test was conducted before colonoscopy. ROC analysis was reported, but data were extracted for the prespecified 50-ng/ml threshold	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Colonoscopy and flexible sigmoidoscopy were performed in the Endoscopy Unit	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Unclear**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
The median time between faecal immunochemical testing and colonoscopy was 9 days (range 1–112 days); 265 declined to participate, 15 completed faecal immunochemical testing only, 138 completed endoscopy only, 30 did not complete faecal immunochemical testing/endoscopy, 11 excluded (faecal immunochemical testing completed after endoscopy/sample not dated/sample arrived after endoscopy)	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	No
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Mowat 2015[52]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
All adult patients referred for investigation of bowel symptoms over a 6-month period	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Adult patients referred (straight to endoscopy or outpatient clinic followed by referral to endoscopy) by GP for investigation of bowel symptoms, who returned faecal tests (1043/2173) and underwent lower endoscopy. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding). The low rate of return may mean that included participants are not representative of those who would undergo the test in practice	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected samples from a single faeces, which were returned to the GP surgery at room temperature and stored at 4 °C (FHb) or –20 °C (FC) prior to analysis to ensure stability. FHb measurement was performed using a single OC-Sensor IO analyser. Any FHb sample that was reported by the analytical system as a positive numerical result of > 0 mg/g was considered as a 'detectable FHb'. Samples with results above the upper analytical limits were not diluted and reassayed but reported as greater than that upper concentration limit. FHb results were converted from the instrument-generated 'ng/ml' to the internationally recommended unit of 'mg/g' by multiplying by 0.2. The laboratory has a total quality management system in place and is accredited to ISO 15189-based standards	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

FC, faecal calprotectin; FHb, faecal haemoglobin.

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Patients referred to endoscopy were investigated within 6 weeks of referral. The endoscopy units participate in the accreditation scheme of the Joint Accreditation Group on GI Endoscopy. Participating clinicians and endoscopists were blind to the faecal test results. All findings were recorded on the endoscopy reporting system by the endoscopist. The diagnoses of CRC, HRA and IBD were confirmed following assessment by a GI pathologist	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Patients referred for endoscopy were investigated within 6 weeks of referral; 1003 patients not returning the faecal test, 114 patients not referred by GP, 18 patients with a cancelled referral, 60 patients cancelling or not attending endoscopy, 78 patients referred to outpatients but not referred for endoscopy	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

Rodríguez-Alonso 2015[53]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Symptomatic, adult patients referred for diagnostic colonoscopy	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Symptomatic adult patients referred for colonoscopy. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding); 66.3% of participants were referred from primary care	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected single faecal samples and were asked to store the sample at < 4 °C and to return it within 7 days. Samples were analysed using OC-Sensor and a MICRO desktop analyser (Eiken). The index test was conducted before colonoscopy	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Colonoscopies were performed by experienced endoscopists who were blind to FIT results	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Time to colonoscopy was determined by the level of Hb detected and NICE/SIGN guidelines. All colonoscopies were completed within 16 weeks; 19 patients not returning the faecal test were excluded from the study; 22 patients with incomplete colonoscopy, and 10 patients who did not attend for colonoscopy, were excluded from the analyses	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	No
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Low**

Terhaar sive Droste 2011[58]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
All adult patients referred for colonoscopy to one of five hospitals in the Netherlands; subgroup data for symptomatic patients were provided by the lead author	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Symptomatic adult patients referred for colonoscopy. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding). Testing was conducted after referral for colonoscopy	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
Patients collected a sample on the day before colonoscopy and before the start of bowel preparation. Samples were stored at –5 °C and analysed within 1 week. Technicians performing FIT analyses were blind to clinical data	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
Endoscopists were blinded to the results of faecal immunochemical testing	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
Colonoscopy was conducted 1 day after faecal immunochemical testing. Patients with incomplete colonoscopy or inadequate bowel cleansing, as judged by the endoscopist (number not reported), were excluded from the analyses	
Was there an appropriate time interval between the index test and reference standard?	Yes
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: Unclear**

Thomas 2016[75]

DOMAIN 1: PATIENT SELECTION

A. RISK OF BIAS	
Symptomatic patients were recruited after their first 2-week wait clinic; 64 patients were excluded after faecal immunochemical testing (no reason reported)	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case–control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Symptomatic adults, tested after referral to secondary care	
Do the included patients match the question?	**Concerns: High**

DOMAIN 2: INDEX TEST(S)

A. RISK OF BIAS	
No details of sample collection or storage/processing were reported. The cut-off point was predefined as the lower limit of the assay. CT/colonoscopy was conducted after faecal immunochemical testing	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it prespecified?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**RISK: Low**
B. APPLICABILITY	
Are there concerns that the index test, its conduct or interpretation differ from the review question?	**Concerns: Low**

DOMAIN 3: REFERENCE STANDARD

A. RISK OF BIAS	
CT/colonoscopy, no further details reported	
Is the reference standard likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct or its interpretation have introduced bias?	**RISK: Unclear**
B. APPLICABILITY	
Is there concern that the target condition, as defined by the reference standard, does not match the review question?	**Concerns: Low**

DOMAIN 4: FLOW AND TIMING

A. RISK OF BIAS	
The time between faecal immunochemical testing and colonoscopy was not reported; 259 patients not returning the faecal test were excluded from the study, 64 patients were excluded after faecal testing (no reason for exclusion was reported and it was unclear whether these patients underwent colonoscopy)	
Was there an appropriate time interval between the index test and reference standard?	Unclear
Did all patients receive a reference standard?	Unclear
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the patient flow have introduced bias?	**RISK: High**

B. PROBAST assessments

Cubiella 2015 (COLONPREDICT)[73] and personal communication, ahead of publication*

(*Callum Fraser, personal communication.)

DOMAIN 1: Participant selection			
A. Risk of bias			
Describe the sources of data and criteria for participant selection: The development cohort consisted of consecutive, symptomatic patients included in a previous diagnostic accuracy study.[55] The validation cohort consisted of patients included in four further published studies,[13,52,53,56] plus an additional unpublished cohort. FIT assay methods differed between studies and within the unpublished cohort			
		Dev	**Val**
1. Were participants defined and assessed in a similar way to participants in the model development study?			No
2. Were appropriate data sources used, e.g. cohort, RCT or nested case–control study data?		Yes	Yes
3. Were all inclusions and exclusions of participants appropriate?		Yes	Yes
Risk of bias introduced by selection of participants	RISK: (*low/high/unclear*)	**Low**	**Low**
Rationale of bias rating: FIT assay methods differed between studies and within the unpublished cohort used in validation. However, the effect of different assay methods on risk score performance was assessed			
B. Applicability			
Describe included participants, setting and dates: Symptomatic adult patients referred for colonoscopy. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding). Not all participants were referred from primary care			
Concern that the included participants and setting do not match the review question	**CONCERN:** (*low/high/unclear*)	**High**	**High**
Rationale of applicability rating: The study population is not a complete match for that specified in the scope for this assessment			

DOMAIN 2: Predictors

A. Risk of bias

List and describe predictors included in the final model, e.g. definition and timing of assessment: Sex, age (continuous variable) and 'µg Hb/g faeces' (categorical: undetectable, 0–19, 20–199 and ≥ 200). No further details were reported. Colonoscopy was conducted after faecal immunochemical testing

		Dev	Val
1. Were predictors defined and assessed in a similar way for all participants?		Yes	No
2. Were predictors defined and assessed in a similar way to predictors in the development model?			No
3. Were predictor assessments made without knowledge of outcome data?		Yes	Yes
4. Are all predictors available at the time the model is intended to be used?		Yes	Yes
Risk of bias introduced by predictors or their assessment	**RISK:** (*low/high/unclear*)	**High**	**High**

Rationale of bias rating: FIT methods used in validation differed from those used in development

B. Applicability

Concern that the definition, assessment or timing of predictors in the model do not match the review question	**CONCERN:** (*low/high/unclear*)	**High**	**High**

Rationale of applicability rating: Faecal immunochemical testing used OC-Sensor, but was undertaken after patients had already been referred for colonoscopy

DOMAIN 3: Outcome

A. Risk of bias

Describe the outcome and how it was defined and determined: Models were reported for the outcomes CRC and advanced neoplasia, both determined by colonoscopy. The definition of advanced neoplasia varied between the studies used in the validation cohort

		Dev	Val
1. Was the outcome determined appropriately?		Yes	Yes
2. Was a prespecified or standard outcome definition used?		Yes	No
3. Were predictors excluded from the outcome definition?		Yes	Yes
4. Was the outcome defined and determined in a similar way for all participants?		Yes	No
5. Was the outcome defined and determined in a similar way to the outcome in the model development study?			No
6. Was the outcome determined without knowledge of predictor information?		Unclear	Unclear
Risk of bias introduced by the outcome or its determination	**RISK:** (*low/high/unclear*)	**Low**	**High**

Rationale of bias rating: The definition of HRA varied between the studies used in the validation cohort.

B. Applicability

At what time point was the outcome determined: The time point at which the outcome was determined varied between studies, but all colonoscopies were completed within 16 weeks

If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome: NA

Concern that the outcome, its definition, timing or determination do not match the review question	**CONCERN:** (*low/high/unclear*)	**Low**	**Low**

Rationale of applicability rating:

NA, not applicable.

DOMAIN 4: Sample size and participant flow

Risk of bias

Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor: 1572 participants were included in the development sample and 3976 in the validation sample. The number of candidate variables and total number of participants with the outcome were not reported

Describe the time interval between predictor assessment and outcome determination: The time between predictor and outcome assessment varied between studies included in the validation cohort, but the maximum time between predictor assessment and outcome determination was 16 weeks

Describe any participants who were excluded from the analysis: Participants who did not complete faecal immunochemical testing or colonoscopy were excluded

Describe missing data on predictors and outcomes, as well as methods used for missing data: No details were reported

		Dev	Val
1. Were there a reasonable number of participants with the outcome?		Unclear	Unclear
2. Was the time interval between predictor assessment and outcome determination appropriate?		Yes	Yes
3. Were all enrolled participants included in the analysis?		No	No
4. Were participants with missing data handled appropriately?		Unclear	Unclear
Risk of bias introduced by sample size or participant flow	**RISK:** (*low/high/unclear*)	**Unclear**	**Unclear**

Rationale of bias rating: Modelling methods were not reported in sufficient detail to adequately assess risk of bias

DOMAIN 5: Analysis

Risk of bias

Describe how the model was developed (predictor selection, optimism, risk groups, model performance): No details reported

Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants): The external validation cohort comprised five different studies, which were separate from the study used as the development cohort

Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit: R2 (measure of variation), Akaike information criterion and Bayesian information criterion. The study describes the diagnostic accuracy of a risk score based on the model results

		Dev	Val
1. Were continuous and categorical predictors handled appropriately?		Yes	
2. Was selection of predictors based on univariable analysis avoided?		Unclear	
3. Were any complexities in the data (e.g. competing risks, multiple events per individual) accounted for appropriately?		Unclear	Unclear
4. Were relevant model performance measures evaluated, e.g. (re)calibration and discrimination?		Unclear	Unclear
5. Was model overfitting and optimism in model performance accounted for?		Unclear	
6. Do predictors and their assigned weights in the final model correspond with the results from multivariable analysis?		Unclear	
Risk of bias introduced by the analysis	**RISK:** (*low/high/unclear*)	**Unclear**	**Unclear**

Rationale of bias rating: Modelling methods were not reported in sufficient detail to adequately assess the risk of bias

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	**RISK:** (*low/high/unclear*)	**High**

Summary of sources of potential bias: Modelling methods were not reported in sufficient detail to adequately assess the risk of bias; however, faecal immunochemical testing methods and advanced neoplasia definitions varied between the studies included in the validation cohort

Overall judgement of applicability	**CONCERN:** (*low/high/unclear*)	**High**

Summary of applicability concerns: The study population is not a complete match for that specified in the scope for this assessment

Rodríguez-Alonso 2015[53]

DOMAIN 1: Participant selection

A. Risk of bias

Describe the sources of data and criteria for participant selection: Participants were patients included in prospective diagnostic accuracy study. The study included patients aged > 18 years, referred for diagnostic colonoscopy between September 2011 and October 2102. Patients referred for adenoma surveillance or post-surgical surveillance of CRC, and those with a history of previous colectomy, IBD or polyp syndromes were excluded. Diagnosis was established by colonoscopy. Validation of the model used a split sample procedure

		Dev	Val
1. Were participants defined and assessed in a similar way to participants in the model development study?			Yes
2. Were appropriate data sources used, e.g. cohort, RCT or nested case–control study data?		Yes	Yes
3. Were all inclusions and exclusions of participants appropriate?		Yes	Yes
Risk of bias introduced by selection of participants	**RISK:** (*low/high/unclear*)	**Low**	**Low**

Rationale of bias rating:

B. Applicability

Describe included participants, setting and dates: Symptomatic adult patients referred for colonoscopy. Symptoms included some not specified in NG12[1] (e.g. rectal bleeding); 66.3% of participants were referred from primary care

Concern that the included participants and setting do not match the review question	**CONCERN:** (*low/high/unclear*)	**High**	**High**

Rationale of applicability rating: The study population is not a complete match for that specified in the scope for this assessment

DOMAIN 2: Predictors

A. Risk of bias

List and describe predictors included in the final model, e.g. definition and timing of assessment: Male gender, iron-deficiency anaemia (not defined) and Hb level ≥ 10 µg/g faeces were included in the final model for CRC. No further details were reported. Colonoscopy was conducted after faecal immunochemical testing and other initial assessments, and endoscopists were blinded to test results

		Dev	Val
1. Were predictors defined and assessed in a similar way for all participants?		Unclear	Unclear
2. Were predictors defined and assessed in a similar way to predictors in the development model?			Unclear
3. Were predictor assessments made without knowledge of outcome data?		Yes	Yes
4. Are all predictors available at the time the model is intended to be used?		Yes	Yes
Risk of bias introduced by predictors or their assessment	**RISK:** (*low/high/unclear*)	**Unclear**	**Unclear**

Rationale of bias rating: Reporting of the model development and validation methods was limited

B. Applicability

Concern that the definition, assessment or timing of predictors in the model do not match the review question	**CONCERN:** (*low/high/unclear*)	**High**	**High**

Rationale of applicability rating: Faecal immunochemical testing used OC-Sensor, but was undertaken after patients had already been referred for colonoscopy and attended an assessment appointment

DOMAIN 3: Outcome

A. Risk of bias

Describe the outcome and how it was defined and determined: Models were reported for the outcomes CRC and advanced neoplasia, both determined by colonoscopy. Advanced neoplasia was defined as CRC or HRA (lesion ≥ 10-mm diameter, villous component or high-grade dysplasia). Endoscopists were blinded to test results

		Dev	Val
1. Was the outcome determined appropriately?		Yes	Yes
2. Was a prespecified or standard outcome definition used?		Yes	Yes
3. Were predictors excluded from the outcome definition?		Yes	Yes
4. Was the outcome defined and determined in a similar way for all participants?		Yes	Yes
5. Was the outcome defined and determined in a similar way to the outcome in the model development study?			Yes
6. Was the outcome determined without knowledge of predictor information?		Yes	Yes
Risk of bias introduced by the outcome or its determination	**RISK:** (*low/high/unclear)*	**Low**	**Low**

Rationale of bias rating:

B. Applicability

At what time point was the outcome determined: All colonoscopies were completed within 16 weeks

If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome: NA

Concern that the outcome, its definition, timing or determination do not match the review question	**CONCERN:** (*low/high/unclear*)	**Low**	**Low**

Rationale of applicability rating:

NA, not applicable.

DOMAIN 4: Sample size and participant flow

Risk of bias

Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor: 680 participants were included in the development sample and 323 in the validation sample. There were 14 candidate variables in the initial analysis. A total of 30 study participants had CRC and 133 had advanced neoplasia

Describe the time interval between predictor assessment and outcome determination: The maximum time between predictor assessment and outcome determination was 16 weeks

Describe any participants who were excluded from the analysis: Participants who did not complete faecal immunochemical testing or colonoscopy were excluded

Describe missing data on predictors and outcomes, as well as methods used for missing data: No details were reported

		Dev	Val
1. Were there a reasonable number of participants with the outcome?		Unclear	Unclear
2. Was the time interval between predictor assessment and outcome determination appropriate?		Yes	Yes
3. Were all enrolled participants included in the analysis?		No	No
4. Were participants with missing data handled appropriately?		Unclear	Unclear
Risk of bias introduced by sample size or participant flow	**RISK:** (*low/high/unclear*)	**Unclear**	**Unclear**

Rationale of bias rating: Modelling methods were not reported in sufficient detail to adequately assess risk of bias

DOMAIN 5: Analysis

Risk of bias

Describe how the model was developed (predictor selection, optimism, risk groups, model performance): A multivariate analysis based on forward conditional logistic regression was performed. Factors were included in the multivariate models, based on based on their univariate association with CRC or advanced neoplasia ($p < 0.05$). Factors not reaching statistical significance were also included if they were judged to be 'clinically relevant or biologically plausible'

Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants): The internal validity of the model was assessed using a random split sampling technique. No further details were reported

Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit: Not reported; the study describes the diagnostic accuracy of a risk score based on the model results

		Dev	Val
1. Were continuous and categorical predictors handled appropriately?		Unclear	
2. Was selection of predictors based on univariable analysis avoided?		No	
3. Were any complexities in the data (e.g. competing risks, multiple events per individual) accounted for appropriately?		Unclear	Unclear
4. Were relevant model performance measures evaluated, e.g. (re)calibration and discrimination?		Unclear	Unclear
5. Was model overfitting and optimism in model performance accounted for?		Unclear	
6. Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?		Unclear	
Risk of bias introduced by the analysis	**RISK:** (*low/high/unclear*)	**High**	**High**

Rationale of bias rating: Modelling methods were not reported in sufficient detail to adequately assess the risk of bias; however, selection of predictors based on univariate analysis was reported

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	**RISK:** (*low/high/unclear*)	**High**
Summary of sources of potential bias: Modelling methods were not reported in sufficient detail to adequately assess the risk of bias; however, selection of predictors based on univariate analysis was reported		
Overall judgement of applicability	**CONCERN:** (*low/high/unclear*)	**High**
Summary of applicability concerns: The study population is not a complete match for that specified in the scope for this assessment		

Appendix 4 Excluded studies

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

- *Population* Adults (≥ 18 years of age) presenting with symptoms suggestive of possible CRC.
- *Setting* Primary care.
- *Index test* Quantitative faecal immunochemical testing [OC-Sensor, HM-JACKarc, FOB Gold, RIDASCREEN Hb (R-Biopharm, Darmstadt, Germany), RIDASCREEN Hb/Hp complex].
- *Reference standard* Colonoscopy.
- *Outcome* Sufficient data to construct 2 × 2 table of test performance.

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

TABLE 67 Details of excluded studies with rationale for exclusion

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

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Chiang TH, Lee YC, Tu CH, Chiu HM, Wu MS. Immunochemical FOBT was accurate for detecting colorectal cancer but less so for other GI lesions. *Ann Intern Med* 2012;**156**:JC2–10	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Screening with qualitative FIT
Chiu HM, Wu MS, Lee YC, Liao WC, Wang HP, Lin JT. Fecal immunochemical test has lower performance in detecting early and proximal advanced colorectal neoplasm. *Gastroenterology* 2012;**142**(5 Suppl. 1):145	Yes	No	No	No	Yes	Yes	Not a symptomatic population Screening population
Cole SR, Upton J, Lane JM, Young GP. A faecal immunochemical test for haemoglobin using a single stool sample is effective for detecting significant colorectal neoplasia. *J Gastroenterol Hepatol* 2009;**24**:A239	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Unclear population, all patients scheduled for colonoscopy No relevant FIT
Crouse AL, De Koning L, Sadrzadeh SM, Naugler C. Sensitivity and specificity of community fecal immunotesting screening for colorectal carcinoma in a high-risk Canadian population. *Arch Pathol Lab Med* 2015;**139**:1441–5	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Screening population
Dutta AK, Alagammai P, Chowdhury SD, Chacko A. Preprocedure haemoglobin and fecal occult blood testing for optimising colonoscopy rates in a resource limited setting for diagnosing colonic malignancy. *Gastrointest Endosc* 2012;**75**(4 Suppl. 1): AB325–6	Yes	No	Unclear	No	Yes	No	Not a symptomatic population gFOBT only, test performance only reported for combined gFOBT and anaemia
Fenocchi E, Gaggero P, Rondan M, Lopez-Alvarenga JC, Sobrino-Cossio S, Lambert N, *et al.* Usefulness of the fecal immunochemical test in the detection of advanced adenomas in subjects at average risk for colorectal cancer. *Endoscopia* 2015;**27**:64–8	Yes	Yes	Unclear	Yes	Yes	No	No relevant outcomes Separate data for symptomatic and asymptomatic patients Reported outcome was mean FIT level for different adenoma sizes
Gillberg A, Ericsson E, Granstrom F, Olsson LI. A population-based audit of the clinical use of faecal occult blood testing in primary care for colorectal cancer. *Colorectal Dis* 2012;**14**:e539–46	Yes	Unclear	Unclear	No	No	Yes	No relevant index test Retrospective study, Symptoms data collected only for those patients with a diagnosis of CRC

continued

TABLE 67 Details of excluded studies with rationale for exclusion (*continued*)

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

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Kalimutho M, Del Vecchio Blanco G, Cretella M, Mannisi E, Sileri P, Formosa A, *et al.* A simplified, non-invasive fecal-based DNA integrity assay and iFOBT for colorectal cancer detection. *Int J Colorectal Dis* 2011;**26**:583–92	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Qualitative FIT
Kaul A, Shah A, Magill FH, Hawkins SA, Skaife P. Immunological faecal occult blood testing: a discriminatory test to identify colorectal cancer in symptomatic patients. *Int J Surg* 2013;**11**:329–31	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Qualitative FIT
Kennell M, Antle S, Hammond M, Stone S, Mahar D, Randell E. Evaluation of the analytical and diagnostic performance of the iFOBT NS-Plus system for use in a province-wide colorectal cancer screening program. *Clin Biochem* 2012;**45**:1116	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Qualitative FIT
Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003;**115**:111–14	Yes	No	Unclear	No	No	No	Not a symptomatic population Screening with qualitative FIT
Kovarova JT, Zavoral M, Zima T, Zak A, Kocna P, Kohout P, *et al.* Improvements in colorectal cancer screening programmes – quantitative immunochemical faecal occult blood testing – how to set the cut-off for a particular population. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2012;**156**:143–50	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic, previous CRC, family history (32% symptomatic) – *authors contacted, reply received stating that subgroup data are not available*
Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. *BMJ* 1983;**286**:673–4	Yes	Yes	Yes	No	No	Yes	No relevant index test gFOBT only – reference standard proctosigmoidoscopy and double-contrast barium enema (colonoscopy in patients with normal findings on these tests who had positive FOBT results)
Leodolter A, Zielinski D, Vieth M, Labenz J. Comparison of different immunological FOBTs for colorectal cancer screening: wide range of sensitivity between different rapid tests. *Gastroenterology* 2010;**138**(5 Suppl. 1):S159	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic (approximately 66% symptomatic) – *authors contacted, no reply received*

continued

TABLE 67 Details of excluded studies with rationale for exclusion (*continued*)

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Levi Z, Hazazi R, Rozen P, Vilkin A, Waked A, Niv Y. A quantitative immunochemical faecal occult blood test is more efficient for detecting significant colorectal neoplasia than a sensitive guaiac test. *Aliment Pharmacol Ther* 2006;**23**:1359–64	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population Asymptomatic screening
Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, *et al.* A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med* 2007;**146**:244–55	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population symptomatic and asymptomatic screening or high risk (47% symptomatic) – *authors contacted, no reply received*[a]
Levi Z, Rozen P, Hazazi R, Vilkin A, Waked A, Maoz E, *et al.* Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. *Am J Gastroenterol* 2009;**104**:933–8	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, increased risk and mildly symptomatic, proportions not specified – *authors contacted, no reply received*[a]
Levy BT, Bay C, Xu Y, Daly JM, Bergus G, Dunkelberg J, *et al.* Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. *J Med Screen* 2014;**21**:133–43	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population (symptomatic, screening or surveillance), proportion not reported No relevant FIT technology
Luthgens K, Maier A, Kampert I, Sieg A, Schmidt-Gayk H. Hemoglobin-haptoglobin-complex: a highly sensitive assay for the detection of fecal occult blood. *Clin Lab* 1998;**44**:543–51	Yes	Unclear	Unclear	No	Yes	Yes	No relevant index test Participants from a gastroenterological practice; unclear if symptomatic Study is of a development version of the test, not that which is currently marketed
McDonald R, Tomlins A, Smith S, Harmston C. Outcomes of faecal occult blood tests requested outside the UK National Bowel Cancer Screening Programme. *J Clin Pathol* 2013;**66**:330–4	Yes	Unclear	Unclear	No	NA	No	No relevant index test Unclear population, survey of testing requests before and after introduction of screening

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Miyoshi H, Oka M, Sugi K, Saitoh O, Katsu K, Uchida K. Accuracy of detection of colorectal neoplasia using an immunochemical occult blood test in symptomatic referred patients: comparison of retrospective and prospective studies. *Intern Med* 2000;**39**:701–6	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Qualitative FIT
Narula N, Ulic D, Al-Dabbagh R, Ibrahim A, Mansour M, Balion C, *et al.* Fecal occult blood testing as a diagnostic test in symptomatic patients is not useful: a retrospective chart review. *Can J Gastroenterol Hepatol* 2014;**28**:421–6	Yes	No	No	No	Yes	Yes	Not a symptomatic population Hospital inpatients, not all symptomatic Type of FOB test not reported
Niv Y, Sperber AD. Sensitivity, specificity, and predictive value of fecal occult blood testing (Hemoccult II) for colorectal neoplasia in symptomatic patients: a prospective study with total colonoscopy. *Am J Gastroenterol* 1995;**90**:1974–7	Yes	Yes	Yes	No	Yes	Yes	No relevant index test gFOBT only
Ogawa M, Iso A, Ootsuka H, Shimizu S, Aoki Y, Tada M, *et al.* [Clinical evaluation of a new immunological fecal occult blood test.] *Ther Res* 1989;**10**:275–82	Yes	No	Unclear	No	No	Yes	No relevant index test Japanese-language publication Qualitative FIT Case–control study
Oono Y, Iriguchi Y, Doi Y, Tomino Y, Kishi D, Oda J, *et al.* A retrospective study of immunochemical fecal occult blood testing for colorectal cancer detection. *Clin Chim Acta* 2010;**411**:802–5	Yes	Yes	Yes	No	Yes	Yes	No relevant index test No relevant FIT technology
Oort FA, Droste JSTS, van Der Hulst RW, Van Heukelem H, Loffeld RJ, Wesdorp EC, *et al.* Flat colonic neoplasia are left undetected by fecal immunochemical tests (FIT) and will be missed in colorectal cancer screening. *Gastroenterology* 2009;**136**(5 Suppl. 1):A113	Yes	Unclear	Unclear	Yes	Yes	No	No relevant outcomes Unclear population, all patients scheduled for colonoscopy No accuracy data
Ou CH, Kuo FC, Hsu WH, Lu CY, Yu FJ, Kuo CH, *et al.* Comparison of the performance of guaiac-based and two immunochemical fecal occult blood tests for identifying advanced colorectal neoplasia in Taiwan. *J Dig Dis* 2013;**14**:474–83	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population (history of CRC or polyp, family history, symptomatic, asymptomatic screening) proportions not reported – *authors contacted, no reply received*

continued

TABLE 67 Details of excluded studies with rationale for exclusion (*continued*)

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Parente FR, Marino B, Perna F, Saracino IM, Zullo A, Hassan C, *et al.* Multiple faecal tests (colon panel) for the detection of colon cancer: a new strategy for appropriate prioritization of screening referrals? Preliminary experience in Italy. *Gastroenterology* 2010;**138**(5 Suppl. 1):192	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACKARC (no longer available in Europe), not HM-JACKarc
Parente F, Marino B, Perna F, Saracino I, Zullo A, Hassan C, *et al.* Multiple faecal tests (colon panel) for the detection of colon cancer: a new strategy for appropriate prioritization of screening referrals? Preliminary experience in Italy. *Dig Liver Dis* 2010;**42**:S86	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACKARC (no longer available in Europe), not HM-JACKarc
Parente F, Marino B, Ilardo A, Fracasso P, Zullo A, Hassan C, *et al.* A combination of faecal tests for the detection of colon cancer: a new strategy for an appropriate selection of referrals to colonoscopy? A prospective multicentre Italian study. *Eur J Gastroenterol Hepatol* 2012;**24**:1145–52	Yes	Yes	Unclear	No	Yes	Yes	No relevant index test – HM-JACKARC (no longer available in Europe), not HM-JACKarc
Piper MA. *Immunochemical versus Guaiac Fecal Occult Blood Tests*. Chicago, IL: Blue Cross and Blue Shield Association, Technology Evaluation Center; 2004	No						Not primary research Provisional DARE abstract, with no publication details
Rae AJ, Cleator IGM. The two-tier fecal occult blood test: cost effective screening. *Can J Gastroenterol* 1994;**8**:362–8	Yes	No	Unclear	No	No	No	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening and surveillance, gFOBT only
Rao S, Forbes G, Venugopal K. High yield for advanced colorectal neoplasia (carcinoma and advanced adenoma) detection with community based faecal immunochemical testing. *J Gastroenterol Hepatol* 2014;**29**:133–4	Yes	No	Unclear	Unclear	Yes	No	Not a symptomatic population Patients referred from primary care because of a positive FIT FIT method not specified
Rodriguez-Moranta F, Ariza X, Berrozpe A, Vazquez X, Binefa G, Navarro M, *et al.* Comparative study of guaiac and quantitative immunochemical fecal occult blood test for colorectal neoplasia. Preliminary results. *Gastroenterology* 2009;**136**(5 Suppl. 1):A623	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening, or surveillance (66% symptomatic). Unspecified FIT – *authors contacted, no reply received*

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, *et al.* Quantitative colonoscopic evaluation of relative efficiencies of a quantified immunochemical fecal occult blood test and a sensitive guaiac test for detecting significant colorectal neoplasms. *Gastroenterology* 2009;**136**(5 Suppl. 1):A113	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Unclear population, 'consecutive ambulatory colonoscopy patients, some above average risk'– *authors contacted, no reply received*[a]
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, *et al.* Identification of colorectal adenomas by a quantitative immunochemical faecal occult blood screening test depends on adenoma characteristics, development threshold used and number of tests performed. *Aliment Pharmacol Ther* 2009;**29**:906–17	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and high risk asymptomatic (59% symptomatic) – *authors contacted, no reply received*[a]
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, *et al.* Colonoscopic evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Gastroenterology* 2009;**136**(5 Suppl. 1):A624	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Unclear population, 'consecutive ambulatory colonoscopy patients, some above average risk'– *authors contacted, no reply received*[a]
Rozen P, Levi Z, Hazazi R, Waked A, Vilkin A, Maoz E, *et al.* Quantitative colonoscopic evaluation of relative efficiencies of an immunochemical faecal occult blood test and a sensitive guaiac test for detecting significant colorectal neoplasms. *Aliment Pharmacol Ther* 2009;**29**:450–7	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic screening or high risk (23% symptomatic) – *authors contacted, no reply received*[a]
Rozen P, Comaneshter D, Levi Z, Hazazi R, Vilkin A, Maoz E, *et al.* Cumulative evaluation of a quantitative immunochemical fecal occult blood test to determine its optimal clinical use. *Cancer* 2010;**116**:2115–25	Yes	No	No	Yes	Yes	Yes	Not a symptomatic population Screening asymptomatic
Sailer M. [A quantitative immunological fecal occult blood test in colorectal neoplasia.] *Coloproctology* 2010;**32**:68–70	No						Not primary research Journal club, screening
Sailer M. [The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer.] *Coloproctology* 2013;**35**:148–50	No						Not primary research Journal club, screening

continued

TABLE 67 Details of excluded studies with rationale for exclusion (*continued*)

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Sieg A, Scheida M, John MR, Hertel A, Schroter M, Luthgens K, *et al.* Validity of new immunological human fecal hemoglobin and albumin tests in detecting colorectal neoplasms – an endoscopy-controlled study. *Z Gastroenterol* 1998;**36**:485–90	Yes	Yes	Yes	No	Yes	Yes	No relevant index test Early development paper (not a commercially available test)
Shaw AG, Lund JN, Longman C, Tierney GM, Goddard AF. The misuse of the faecal occult blood test under the lower gastrointestinal two week wait rule. *Colorectal Dis* 2009;**11**:94–6	Yes	Yes	Yes	No	NA	No	No relevant index test Survey of guaiac faecal occult blood testing prior to referral (no test performance data)
Symonds EL, Young GP, Osborne JM, Cole SR, Gopalsamy G, Gaur S, *et al.* Detection of colorectal neoplasia: comparison of a methylated two-gene (BCAT1-IKZF1) blood test with a faecal immunochemical test. *J Gastroenterol Hepatol* 2015;**30**:83	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Mixed population: states 'scheduled for colonoscopy for any reason' but the objective describes test evaluation in 'a patient population exhibiting the full spectrum of pathology encountered in the colon/rectum'– *authors contacted, no reply received*
Tate JJ, Northway J, Royle GT, Taylor I. Faecal occult blood testing in symptomatic patients: comparison of three tests. *Br J Surg* 1990;**77**:523–6	Yes	Yes	Yes	No	No	Yes	No relevant index test gFOBT only Patients referred for double-contrast barium enema (reference standard), assumed by the authors to be symptomatic
Thomas WM, Hardcastle JD, Jackson J, Pye G. Chemical and immunological testing for faecal occult blood: a comparison of two tests in symptomatic patients. *Br J Cancer* 1992;**65**:618–20	Yes	Yes	Yes	No	Yes	No	No relevant index test Only sensitivity data reported
Tibble J, Sigthorsson G, Foster R, Sherwood R, Fagerhol M, Bjarnason I. Faecal calprotectin and faecal occult blood tests in the diagnosis of colorectal carcinoma and adenoma. *Gut* 2001;**49**:402–8	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population, healthy controls, known CRC and referred patients (symptomatic and polyp surveillance, proportions not specified) No relevant FIT technology

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Tsumuraya M, Noda A, Tsubura S, Sugimoto K, Minowa M, Seki T, *et al.* [Comparative clinical study of 'Monohem' and four reagents for faecal occult blood test.] *Ther Res* 1989;**10**(Suppl. 1):87–95	Yes	No	Unclear	No	No	Yes	No relevant index test Japanese-language publication Qualitative FIT Case–control study
University of Aarhus. *A Trial of the Implementation of iFOBT in General Practice.* NCT02308384. International Clinical Trials Registry Platform. Geneva: World Health Organization; 2014. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02308384 (accessed 9 March 2016)	Yes	Yes	Yes	Unclear	NA	No	No relevant outcomes Ongoing study, behavioural intervention for GPs
University of Malaya. *Quantitative Versus Qualitative Fecal Immunochemical Tests (FIT) to Prioritize Urgency of Colonoscopy Referral.* NCT02037646. International Clinical Trials Registry Platform. Geneva: World Health Organization; 2014. URL: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02037646 (accessed 9 March 2016)	Yes	No	No	Unclear	Yes	Yes	Not a symptomatic population Screening study, index test and comparator unclear
Uppsala University. *Quantitative Immunochemical Fecal Occult Blood Test in Symptomatic Patients.* NCT02491593. ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2015. URL: https://ClinicalTrials.gov/show/NCT02491593 (accessed 9 March 2016)	Yes	Yes	Yes	Unclear	Unclear	Yes	No data available Ongoing study, potentially relevant Unclear intervention, quantitative FIT Unspecified reference standard
van Turenhout ST, Van Rossum LG, Oort FA, Laheij RJ, Van Rijn AF, Fockens P, *et al.* Differences in FIT results between screening and referred colorectal cancer patients are explained by differences in tissue tumor stage. *Gastroenterology* 2010;**138**(5 Suppl. 1):185	Yes	No	Unclear	Yes	Yes	No	Not a symptomatic population Comparison of stages of CRC between screening detected and symptomatic patients
Viana Freitas BR, Kibune Nagasako C, Pavan CR, Silva Lorena SL, Guerrazzi F, Saddy Rodrigues Coy C, *et al.* Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. *Gastroenterol Res Pract* 2013; 384561	Yes	No	No	No	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic high risk, or surveillance Qualitative FIT

continued

TABLE 67 Details of excluded studies with rationale for exclusion (*continued*)

Study details	Primary study	Population	Setting	Index test	Reference standard	Outcome	Reason for exclusion and comments
Vilkin A, Rozen P, Levi Z, Waked A, Maoz E, Birkenfeld S, *et al.* Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol* 2005;**100**:2519–25	Yes	No	Yes	Yes	Yes	Yes	Not a symptomatic population Mixed population, symptomatic and asymptomatic high risk (approximately 73% symptomatic) – *authors contacted, no reply received*[a]
Vogel T, Driemel C, Hauser A, Hansmann A, Lange S, Jonas M, *et al.* [Comparison of different stool tests for the detection of cancer of the colon.] *Dtsch Med Wochenschr* 2005;**130**:872–7	Yes	No	No	No	Yes	Yes	Not a symptomatic population Includes health control participants No relevant FIT technology
Wakamura K, Kudo SE, Ikehara N, Mori Y, Hayashi S, Takeda K, *et al.* A prospective evaluation using the colonoscope of the fecal occult blood test-negative colorectal neoplasms in a referral hospital. *Gastrointest Endosc* 2012;**75**(4 Suppl. 1):AB343–4	Yes	No	Unclear	No	Yes	Yes	Not a symptomatic population Mixed population (approximately 25% symptomatic). Unspecified FIT method – *authors contacted, reply received* No relevant FIT technology
De Wijkerslooth TR, Stoop EM, Bossuyt PM, Meijer GA, van Ballegooijen M, van Roon AH, *et al.* Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. *Am J Gastroenterol* 2012;**107**:1570–8	Yes	No	Unclear	Yes	Yes	Yes	Not a symptomatic population Asymptomatic screening
Williams JA, Hunter R, Coles ME, Thomas DW, Huber TW. An assessment of an immunochemical test for human haemoglobin in the detection of colonic polyps. *Aust N Z J Surg* 1985;**55**:485–8	Yes	No	Unclear	Unclear	Yes	No	Not a symptomatic population Mixed population symptomatic and asymptomatic, or history of CRC (proportions not reported) FIT type not reported
Wong BC, Wong WM, Cheung KL, Tong TS, Rozen P, Young GP, *et al.* A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003;**18**:941–6	Yes	No	Unclear	No	Yes	No	Not a symptomatic population Mixed population, symptomatic and asymptomatic surveillance (46% symptomatic) FlexSure OBT and Hemoccult SENSA, no relevant FIT technology Only sensitivity data reported

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

a P Rozen is now deceased; co-authors were contacted.

Appendix 5 Excluded studies (cost-effectiveness review)

TABLE 68 Details of studies excluded from the cost-effectiveness review

Author Year	Country	Summary of model	Intervention/ comparator	Patient population	QALYs	Costs	ICER	Sensitivity analyses
Allen 2005[109]	USA • Modified societal perspective (no indirect costs, no costs of other care due to undiagnosed disease) • Time horizon: lifetime	Decision tree and Markov model; prevalence of serious disease in patients with rectal bleeding obtained from systematic review; estimates of specificity and sensitivity obtained from review of prospective diagnostic studies; utilities obtained from different studies; instruments CRC/HUI, univariate and multivariate sensitivity analysis; discount rate 3%	• WW • FS • FS+ACBE • colonoscopy	Patients aged ≥ 40 years, with otherwise asymptomatic rectal bleeding	• FS: 14.876 • Colonoscopy: 14.890 • FS+ACBE: 14.885 • WW: 14.665	• FS: US$17,100 • Colonoscopy: US$17,200 • FS+ACBE: US$17,300 • WW: US$17,500	• Colonoscopy compared with FS: US$5480 • FS-ACBE compared with FS: US$25,107 • WW vs. colonoscopy: dominated • FS-ACBE vs. colonoscopy: dominated	The ICER was affected by different variables: age, prevalence of polyps, costs of colonoscopy, charges of procedures
Rae 1994[110]	Canada/USA	No model	Different FOBTs: • Hemoccult • HO Sensa, HemeSelect • Two-tier tests (including HO sense followed by HemeSelect)	Patients ≥ 40 years • First arm: high-risk group, referred to a gastroenterologist for large bowel work-up • Second arm: visiting a physician for routine physical examination or surveillance follow-up after personal history of CRC, polyps or IBD • The second arm is split up in symptomatic and asymptomatic patients	No QALYs Cancer detected: • First arm ($n = 573$): 19 Hemoccult, 20 HO Sensa, 19 HemeSelect, 19 Two-tier test • Second arm ($n = 1301$): 2 Hemoccult, 3 HO Sensa, 2 HemeSelect, 2 Two-tier test • Second arm (asymptomatic $n = 578$): 0 Hemoccult, 1 HO Sensa, 1 HemeSelect, 1 Two-tier test	Total costs (incl. tests and colonoscopy) • First arm: US$44,865 Hemoccult, US$63,512HO Sensa, US$47,223 HemeSelect, US$34,991 two-tier • Second arm (total): US$50,355 Hemoccult, US$81,494 HO Sensa, US$41,895 HemeSelect, US$21,650 two-tier • Second arm (asymptomatic $n = 578$) • US$15,504 Hemoccult, US$25,585 HO Sensa, US$16,422 HemeSelect, US$5476 two-tier	Costs per cancer detected: • First arm: US$2361 Hemoccult, US$3176 HO Sensa, US$2485 HemeSelect, US$1842 two tier • Second arm (total): US$25,178 Hemoccult, US$27,165 HO Sensa, US$20,948 HemeSelect, US$10,825 two-tier • Second arm asymptomatic patients: US$25,585 HO sense, US$16,422 HemeSelect, US$5476 two-tier	NA

FS, flexible sigmoidoscopy; FS+ACBE, flexible sigmoidoscopy followed by air contrast barium enema; HUI, Health Utilities Index; NA, not applicable; WW, watchful waiting.

Appendix 6 Questionnaire and information sent to clinical experts

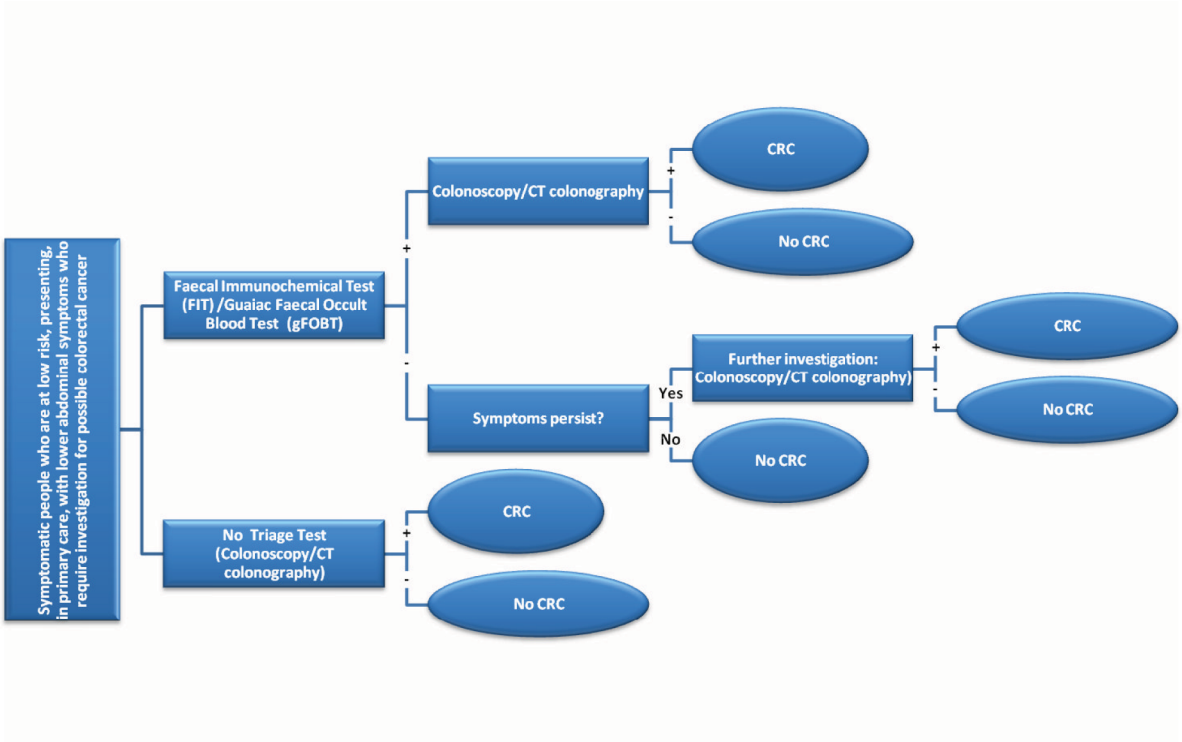
One of the goals of our assessment is to explore the cost-effectiveness of using a quantitative faecal immunochemical test (FIT) for haemoglobin (occult blood) as a triage test in the investigation of symptomatic people presenting in the primary care setting who are at low risk of colorectal cancer (CRC). The cost-effectiveness of FIT will be compared with guaiac faecal occult blood tests (gFOBT) and with no triage (referral straight to colonoscopy).

A health economic model is currently being developed to address the question above. The model consists of two parts:

1. the diagnostic model – a decision tree reflecting the diagnosis of CRC, and
2. the CRC model – a Markov state-transition model to estimate the long-term costs and effects associated with the treatment and progression of CRC.

Information about the diagnostic performance of FIT will be derived from the systematic review component of our assessment; however, additional information about the patient pathway after FIT testing is needed in order to fully populate the model. Specific questions regarding modelling assumptions are listed below. Any information that you are able to provide (from publications, unpublished data or personal experience) would be very much appreciated.

The model begins with a cohort of symptomatic patients, presenting in primary care, who require investigation for possible CRC. A patient in the cohort can have one of the following tests: FIT, gFOBT or no triage testing at all (referral straight to colonoscopy). A positive test will result in referral to colonoscopy while a negative test will result in a watchful waiting strategy in which a repeated test or further investigation can be performed when symptoms persist. A schematic representation of the decision-analytic model is given below:



Patient compliance

1) What percentage of symptomatic patients (not yet referred for colonoscopy) would you expect to return a faecal sample for FIT or gFOBT?

Please provide your answer here:

	Lowest estimate	Most likely estimate	Highest estimate
FIT			
gFOBT			

2) What percentage of patients not returning a sample would then need to be referred to colonoscopy?

Please provide your answer here:

Lowest estimate	Most likely estimate	Highest estimate

3) What percentage of patients do not consent to colonoscopy?

Please provide your answer here:

	Lowest estimate	Most likely estimate	Highest estimate
Of those testing positive with FIT/gFOBT?			
In those referred without triage?			

Colonoscopy versus CT colonography

4) If the gFOBT or FIT result is positive, patients are referred to either colonoscopy or CT colonography (CTC). What would be the (estimated) percentage of patients that receive colonoscopy versus CTC in the UK?

Please provide your answer here:

	Lowest estimate	Most likely estimate	Highest estimate
Colonoscopy			
CTC			
Other (please specify)			

Negative test result FIT/gFOBT

5) What percentage of those patients who test negative with FIT/gFOBT will eventually undergo colonoscopy?

Please provide your answer here:

Lowest estimate	Most likely estimate	Highest estimate

6) Could you also estimate the time interval to getting this colonoscopy?

Please provide your answer here:

Lowest estimate	Most likely estimate	Highest estimate

7) What percentage of those patients that test negative with FIT/gFOBT would get a second FIT/gFOBT?

Please provide your answer here:

Lowest estimate	Most likely estimate	Highest estimate

Positive test result FIT/gFOBT

8) What is the average time interval between presentation and colonoscopy?

No triage

9) What is the average time-interval between presentation and colonoscopy?

Positive test result colonoscopy

10) The study population is symptomatic patients at low risk, presenting in primary care, with lower abdominal symptoms, who require investigation for possible CRC. In those who eventually have a colonoscopy and are staged by CT what percentage would be found to be in each of the Dukes' stages (I, II, III, IV)?

Please provide your answer here:

	Lowest estimate	Most likely estimate	Highest estimate
Dukes' stage I			
Dukes' stage II			
Dukes' stage III			
Dukes' stage IV			

Appendix 7 Equations used to estimates probabilities in the diagnostic (decision tree) model

The probabilities used at the decision nodes in the diagnostic model, labelled as (A)–(J) in *Figure 12*, were summarised in *Table 27*. Most of them are functions of the sensitivity and specificity of the tests and the prevalence of the disease in the patient population. In this appendix we provide full derivations of those equations.

(A) Probability that faecal immunochemical test/guaiac faecal occult blood test is positive

By the Law of Total Probability and the definitions of sensitivity, specificity and prevalence, the following holds: P[T+] = P[T+|CRC+] × P[CRC+] + P[T+|CRC–] × P[CRC–] = (sensitivity × prevalence) + [(1 – specificity) × (1 – prevalence)].

(B) Probability that faecal immunochemical test/guaiac faecal occult blood test is negative

This was calculated as 1 – (A).

(C) Probability that colorectal cancer is present after a positive faecal immunochemical test/guaiac faecal occult blood test

This is the definition of the PPV. For the PSA, we assumed a beta distribution on the PPV.

(D) Probability that colorectal cancer is not present after a positive faecal immunochemical test/guaiac faecal occult blood test

This was calculated as 1 – PPV.

(E) Probability that symptoms persist after a negative faecal immunochemical test/guaiac faecal occult blood test

This was estimated based on expert opinion (mean value 0.325). A beta distribution was assumed for the PSA.

(F) Probability that symptoms do not persist after a negative faecal immunochemical test/guaiac faecal occult blood test

This was calculated as 1 – (E).

(G) Probability that colorectal cancer is present for symptomatic patients after a negative faecal immunochemical test/guaiac faecal occult blood test

This was calculated as (1 – NPV)/(E). The full derivation is as follows.

Note that this probability cannot be directly estimated, as we do not have data on the 'specificity' of persisting in symptoms, that is, we have assumed that persisting in symptoms is perfectly sensitive (all patients with CRC with test negative will persist in their symptoms), but there will also be some 'FPs' (patients whose symptoms persist after testing negative that will not have CRC). With the data we have, we can estimate the joint probability of (E) and (G) as follows.

The probability of persisting in symptoms after testing negative was estimated based on expert opinion. This is (E) in the diagnostic model. We denote this probability as P[symp|T–] here. Note that this will include patients with and without CRC (denoted by CRC+ and CRC–, respectively). Therefore, we need to calculate the following probabilities:

- P[symp and CRC+|T–]: probability of remaining symptomatic and CRC+ after testing negative.
- P[symp and CRC–|T–]: probability of remaining symptomatic and CRC– after testing negative.
- P[no symp and CRC+|T–]: probability of becoming asymptomatic and CRC+ after testing negative.
- P[no symp and CRC–|T–]: probability of becoming asymptomatic and CRC– after testing negative.

By the Law of Total Probability, we have that:

$$P[\text{symp}|T-] = P[\text{symp and CRC}-|T-] + P[\text{symp and CRC}+|T-] \quad (3)$$

$$P[\text{no symp}|T-] = P[\text{no symp and CRC}-|T-] + P[\text{no symp and CRC}+|T-]. \quad (4)$$

As we are assuming that P[no symp and CRC+|T–] = 0 (i.e. all patients with CRC remain symptomatic), equation 4 reduces to:

$$P[\text{no symp}|T-] = P[\text{no symp and CRC}-|T-]. \quad (5)$$

Applying the Law of Total Probability again, we have that P[CRC + |T–] = P[symp and CRC+|T–] + P[no symp and CRC+|T–], which also reduces to:

$$P[\text{CRC}+|T-] = P[\text{symp and CRC}+|T-]. \quad (6)$$

Thus, the probability of having CRC given test negative is equal to the probability of being symptomatic and having CRC given test negative (as we had assumed). Rearranging equation 6 and substituting into equation 3, we have that:

$$P[\text{symp and CRC}-|T-] = P[\text{symp}|T-] - P[\text{CRC} + |T-]. \quad (7)$$

As P[CRC+|T–] is defined as 1 – NPV, we can conclude that:

$$P[\text{symp and CRC}+|T-] = 1 - \text{NPV} \quad (8)$$

$$P[\text{symp and CRC}-|T-] = P[\text{symp}|T-] - (1 - \text{NPV}) \quad (9)$$

$$P[\text{no symp and CRC}+|T-] = 0 \quad (10)$$

$$P[\text{no symp and CRC}-|T-] = 1 - P[\text{symp}|T-]. \quad (11)$$

It should be emphasised that equation 8 is the joint probability of (E) and (G); equation 9 is the joint probability of (E) and (H); and equation 10 is the probability (F). Thus, (G) can be estimated as (1 – NPV)/(E).

There are two potential problems here:

As P[symp|T–] was estimated by experts independently of the accuracy estimates of faecal immunochemical testing/gFOBT and the prevalence, it might not be guaranteed that P[symp and CRC–|T–], equation 9, is always positive. Note that the experts estimated the mean P[symp|T–] as 0.325. For example, when the accuracy data from Mowat *et al.*[52] (threshold of 0 µg Hb/g faeces for the detection of CRC using a single faecal sample) was used, the NPV was high enough (0.9948 if based on prevalence in study or 0.9979 if based on 1.5% prevalence) to keep the equation positive, but this would be a problem if the NPV fell below 0.675 (i.e. 1 – 0.325). With the data we have, this is probably not a problem, but particular attention must be taken when the PSA is run.

The second potential problem is that, we have shown that, conditional on testing negative, the probability of remaining symptomatic and having CRC was 1 – NPV. However, as we previously mentioned, that is not the probability needed for the model, we need (G). We have shown above that (G) = (1 – NPV)/P[symp|T–]. This is not a problem when the mode is run deterministically, but having P[symp|T–] in the denominator, which is assumed to follow a beta distribution, causes numerical problems when performing the PSA (numerical division by 0). For that reason, for the PSA, we decided to consider (G) = (1 – NPV)/mean(P[symp|T–]), where mean(P[symp|T–]) = 0.325, given by the experts.

Note, finally, that there should be no uncertainty from being symptomatic in estimating the probability of having the disease given test negative. This is because in equation 8 we concluded that P[symp and CRC+|T–] = 1–NPV. This is the joint probability of (E) and (G), but, in the model, this joint probability is calculated as P[symp|T–] × (1 – NPV)/mean(P[symp|T–]), where P[symp|T–] and mean(P[symp|T–]) do not cancel each other out. Therefore, our model is likely to overestimate the uncertainty around this probability.

(H) Probability that colorectal cancer is not present for symptomatic patients after a negative test

This was calculated as 1 – (G).

(I) Probability that colorectal cancer is present

This was estimated as the prevalence of CRC in our population.

Note that this is equivalent to the probability of having a positive colonoscopy in the no triage (referral straight to colonoscopy) arm of the diagnostic model (thus colonoscopy only). As prevalence is defined as the proportion of the population with the condition and given that we are assuming that colonoscopy is a perfect diagnostic for CRC, the prevalence is indeed the probability that we need. In NG12[1] it was assumed that the prevalence of CRC in the base-case population was 1.5%. This value was obtained from experts. Further, a range of variation was assumed and then a uniform or triangular probability distribution can be used to include this parameter in the PSA.

(J) Probability that colorectal cancer is not present

This was calculated as 1 – (I).

Appendix 8 Annual survival/mortality rates included in the colorectal cancer Markov model

TABLE 69 Predicted 15-year CRC survival probability by Dukes' stage used in NG12[1]

Year	Dukes' A predicted	Dukes' B predicted	Dukes' C predicted	Dukes' D predicted
0	100	100	100	100
1	97.211	92.233	82.357	38.112
2	95.541	85.403	65.111	17.669
3	94.577	81.644	56.749	11.270
4	93.900	79.078	51.476	8.192
5	93.377	77.144	47.725	6.396
6	92.953	75.598	44.865	5.225
7	92.595	74.316	42.581	4.404
8	92.286	73.222	40.696	3.798
9	92.015	72.271	39.103	3.333
10	91.773	71.431	37.731	2.965
11	91.555	70.679	36.532	2.668
12	91.356	70.000	35.470	2.422
13	91.173	69.381	34.520	2.217
14	91.004	68.812	33.664	2.042
15	90.848	68.287	32.886	1.891

TABLE 70 Annual CRC mortality estimates and the parameters of beta distributions used in the PSA

	Dukes' A			Dukes' B			Dukes' C			Dukes' D		
Cycle	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β
1	2.89	793	26610	7.87	5893	68982	17.75	12912	59847	61.99	17551	10761
2	1.83	497	26676	7.52	5198	63945	21.05	12621	47328	53.75	5808	4998
3	1.13	313	27371	4.52	2909	61428	12.96	6162	41374	36.34	1824	3196
4	0.85	241	28240	3.27	2024	59830	9.42	3916	37648	27.45	880	2327
5	0.69	204	29186	2.58	1558	58723	7.42	2808	35026	22.06	515	1820
6	0.60	183	30237	2.15	1273	57938	6.14	2162	33052	18.45	337	1489
7	0.54	170	31403	1.85	1083	57386	5.25	1745	31505	15.87	237	1257
8	0.50	163	32609	1.64	948	56994	4.59	1455	30250	13.93	176	1086
9	0.47	161	34026	1.48	850	56781	4.09	1246	29227	12.42	135	955
10	0.45	162	35556	1.35	777	56700	3.70	1090	28377	11.22	108	852
11	0.44	166	37266	1.26	723	56760	3.39	969	27674	10.24	88	769
12	0.44	174	39221	1.19	684	56977	3.13	876	27103	9.42	73	701
13	0.45	186	41372	1.13	657	57338	2.93	803	26646	8.74	62	644
14	0.46	202	43677	1.09	639	57828	2.76	745	26290	8.16	53	596
15	0.48	220	46085	1.07	629	58432	2.62	699	26025	7.67	46	555
16	0.51	243	47550	1.10	652	58670	2.65	698	25653	7.70	43	516
17	0.54	267	48963	1.13	675	58908	2.68	697	25294	7.74	40	480
18	0.58	294	50384	1.17	701	59173	2.72	698	24959	7.77	38	446
19	0.62	323	51802	1.21	729	59459	2.76	700	24646	7.82	35	415
20	0.66	355	53152	1.25	758	59740	2.80	702	24347	7.86	33	386
21	0.71	389	54452	1.30	790	60022	2.85	705	24064	7.90	31	360
22	0.76	424	55688	1.35	823	60297	2.90	710	23795	7.95	29	335
23	0.81	463	56872	1.40	859	60571	2.95	715	23544	8.00	27	312

	Dukes' A			Dukes' B			Dukes' C			Dukes' D		
Cycle	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β
24	0.86	503	57968	1.45	896	60826	3.00	721	23304	8.06	25	290
25	0.92	547	59016	1.51	936	61081	3.06	728	23084	8.12	24	271
26	0.98	595	60005	1.58	979	61329	3.12	737	22883	8.18	22	252
27	1.06	648	60973	1.65	1028	61593	3.19	749	22714	8.25	21	235
28	1.13	706	61881	1.72	1082	61852	3.27	763	22572	8.33	20	220
29	1.22	773	62754	1.81	1143	62121	3.36	780	22468	8.42	19	205
30	1.32	849	63587	1.92	1214	62401	3.46	803	22412	8.52	18	192
31	1.44	935	64323	2.03	1294	62655	3.58	830	22394	8.63	17	180
32	1.57	1033	64966	2.17	1386	62886	3.71	863	22426	8.77	16	169
33	1.72	1141	65447	2.31	1487	63044	3.86	901	22490	8.92	15	158
34	1.89	1260	65752	2.48	1599	63113	4.03	946	22589	9.09	15	149
35	2.08	1388	65849	2.67	1720	63062	4.22	997	22713	9.27	14	140
36	2.29	1526	65725	2.88	1851	62872	4.43	1054	22860	9.48	14	132
37	2.52	1671	65358	3.11	1989	62515	4.66	1118	23017	9.71	13	125
38	2.77	1827	64751	3.36	2138	61983	4.91	1191	23192	9.97	13	118
39	3.06	1994	63894	3.65	2299	61258	5.20	1274	23382	10.25	13	112
40	3.38	2171	62776	3.97	2470	60319	5.52	1368	23580	10.57	12	106
41	3.75	2362	61387	4.34	2655	59146	5.89	1477	23788	10.94	12	101
42	4.17	2565	59712	4.76	2853	57714	6.31	1602	23989	11.36	12	96
43	4.66	2782	57738	5.25	3064	56000	6.80	1746	24172	11.85	12	92
44	5.22	3010	55452	5.81	3287	53980	7.36	1911	24314	12.41	12	88
45	5.87	3244	52848	6.46	3515	51636	8.00	2097	24377	13.06	13	85
46	6.60	3475	49927	7.19	3741	48962	8.74	2302	24320	13.80	13	81
47	7.44	3694	46708	8.03	3954	45968	9.58	2520	24098	14.64	13	78

continued

TABLE 70 Annual CRC mortality estimates and the parameters of beta distributions used in the PSA (*continued*)

	Dukes' A			Dukes' B			Dukes' C			Dukes' D		
Cycle	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β	Mortality (%)	α	β
48	8.38	3886	43221	8.97	4138	42678	10.52	2743	23663	15.58	14	76
49	9.43	4036	39515	10.02	4280	39139	11.57	2958	22977	16.62	14	73
50	10.57	4131	35654	11.16	4365	35413	12.71	3151	22015	17.76	15	70
51	11.81	4159	31713	12.40	4381	31574	13.95	3307	20771	19.00	16	68
52	13.15	4114	27772	13.74	4322	27708	15.29	3410	19257	20.34	16	65
53	14.60	3997	23912	15.19	4188	23896	16.74	3450	17506	21.79	17	62
54	16.14	3805	20212	16.74	3977	20226	18.28	3413	15569	23.34	18	60
55	17.80	3545	16747	18.39	3697	16774	19.94	3297	13514	24.99	19	57
56	19.55	3228	13580	20.14	3359	13609	21.69	3100	11424	26.74	19	54
57	21.40	2865	10760	21.99	2974	10785	23.54	2830	9385	28.59	20	51
58	23.32	2472	8321	23.91	2561	8340	25.46	2500	7483	30.51	21	48
59	25.29	2071	6273	25.89	2142	6286	27.43	2135	5784	32.49	21	45
60	27.35	1687	4604	27.94	1740	4610	29.49	1764	4329	34.55	21	41
61	29.52	1334	3281	30.11	1374	3283	31.66	1410	3130	36.72	22	38

Appendix 9 Annual mortality rates included in the healthy population Markov model

TABLE 71 Annual mortality rate, by age, used in the healthy population Markov model

Age	Weighted average annual mortality	Beta distribution (α)	Beta distribution (β)
40	0.0010	98,337	101
41	0.0011	98,227	111
42	0.0012	98,109	118
43	0.0013	97,981	127
44	0.0014	97,846	135
45	0.0015	97,704	143
46	0.0016	97,552	152
47	0.0016	97,392	160
48	0.0018	97,220	172
48	0.0018	97,220	172
49	0.0019	97,036	184
50	0.0021	96,836	199
51	0.0023	96,618	218
52	0.0025	96,379	240
53	0.0027	96,115	264
54	0.0030	95,823	291
55	0.0034	95,502	322
56	0.0037	95,148	353
57	0.0041	94,760	388
58	0.0045	94,336	425
59	0.0049	93,873	463
60	0.0054	93,369	503
61	0.0059	92,824	545
62	0.0064	92,235	590
63	0.0069	91,599	635
64	0.0075	90,915	684
65	0.0081	90,180	735
66	0.0088	89,387	793
67	0.0096	88,532	855
68	0.0105	87,608	924
69	0.0115	86,604	1004

continued

TABLE 71 Annual mortality rate, by age, used in the healthy population Markov model (*continued*)

Age	Weighted average annual mortality	Beta distribution (α)	Beta distribution (β)
70	0.0127	85,512	1092
71	0.0140	84,321	1191
72	0.0155	83,021	1299
73	0.0172	81,604	1417
74	0.0191	80,060	1544
75	0.0212	78,382	1678
76	0.0234	76,562	1819
77	0.0260	74,593	1969
78	0.0289	72,465	2129
79	0.0321	70,167	2298
80	0.0358	67,688	2479
81	0.0400	65,016	2672
82	0.0448	62,140	2877
83	0.0505	59,047	3092
84	0.0569	55,734	3313
85	0.0643	52,204	3531
86	0.0727	48,468	3736
87	0.0821	44,553	3914
88	0.0925	40,501	4052
89	0.1040	36,366	4135
90	0.1164	32,212	4154
91	0.1298	28,111	4101
92	0.1442	24,134	3977
93	0.1597	20,352	3782
94	0.1762	16,831	3521
95	0.1938	13,628	3203
96	0.2123	10,786	2842
97	0.2315	8334	2452
98	0.2512	6280	2054
99	0.2718	4607	1673
100	0.2935	3283	1324

Appendix 10 Technical details about parameter estimation

For all input parameters of the model included in the PSA, a certain measure of variation around the mean value is needed. This measure of variation is usually reported as a standard error (SE), 95% CI or 25% and 75% quartiles. With this information, the input parameters of the model can be fit to appropriate probability distributions (e.g. beta for sensitivity and specificity, gamma for costs, etc.) by estimating the parameters of the corresponding probability distributions. For some input parameters of the model (e.g. utilities for Dukes' stages), the parameters of the probability distributions were reported in the literature and included directly in our model.

When the SE is reported, the parameters of a beta distribution can be obtained from the mean and SE as $\alpha = \text{mean} \times [(\text{mean} \times (1 - \text{mean})/(\text{SE})^2) - 1]$ and $\beta = (1 - \text{mean}) \times [(\text{mean} \times (1 - \text{mean})/\text{SE}^2) - 1]$. This is the case for example of the sensitivity for the OC-Sensor. Similarly, the parameters of a gamma distribution can be obtained from the mean and SE as $\alpha = (\text{mean}/\text{SE})^2$ and $\beta = \text{SE}^2/\text{mean}$. This is done, for example, with the costs associated to Dukes' stages.

When a CI or any other uncertainty range is reported, parameter estimation is not as straightforward as in the examples mentioned above, and more complex numerical procedures have to be applied. In those situations, the parameters of the probability distribution functions were estimated in R, version 3.3.1 (The R Foundation for Statistical Computing, Vienna, Austria), using different methods. As probability distribution functions are usually multivariate functions (more than one parameter needs to be estimated), R methods to solve non-linear multivariate equations are preferred. In particular, the R function *nleqslv* (package *nleqslv* – https://cran.r-project.org/web/packages/nleqslv/nleqslv.pdf) was used. However, in some cases, this method did not converge and, therefore, it did not provide a solution. In those situations, after trying some other multivariate methods available in R, which also failed to find a solution, a univariate approach, the function *uniroot* (https://stat.ethz.ch/R-manual/R-devel/library/stats/html/uniroot.html) from the package *stats*, or a simulation approach were used. In this appendix, we describe, with the help of a few examples, the problems encountered and the solutions proposed. Complete results can be found in the file 'Parameter calculator.R'.

Example 1: probability of bleeding

The mean reported was 2.6% and the 95% CI was (1.7% to 3.7%). In this case, the multivariate method *nleqslv* worked well. The idea behind this approach is to find the two parameters α and β such that the 2.5% percentile of a beta distribution is 1.7% and the 97.5% percentile of a beta distribution is 3.7%. This can be expressed in R as the two equations below:

$$F1 = \text{pbeta}(0.0017, x^1, x^2) - 0.025 \quad (12)$$

$$F2 = \text{pbeta}(0.0017, x^1, x^2) - 0.975 \quad (13)$$

These equations were solved with the *nleqslv* function and the solutions obtained were $\alpha = 25.82748$ and $\beta = 9887.901$. The complete R code can be found in the file 'Parameter calculator.R'.

Example 2: sensitivity for the HM-JACKarc system

The sensitivity for HM-JACKarc was obtained from a single study that reported a mean = 1 and 95% CI = (0.715 to 1.00). Because the mean is exactly 1, a beta distribution could not be properly fit. In this case, we used the *uniroot* function because it provided a better fit. However, the mean had to be set to 0.98, otherwise the method would not converge.

The idea behind this approach is to find the parameter α such that the mean of a beta distribution is 0.98 and (for example) the 2.5% percentile of a beta distribution is 0.715 (the 97.5% can also be used). The latter can be expressed in R as the following equation:

$$F1 = \text{pbeta}(0.715, \text{alpha}, \text{beta}) - 0.025. \quad (14)$$

Note also that for the beta distribution the following equation always holds:

$$\beta = (\alpha/\text{mean}) - \alpha. \quad (15)$$

Thus, substitution in F1 above yields:

$$F1 = \text{pbeta}[0.175, \text{alpha}, (\text{alpha}/\text{mean}) - \text{alpha}] - 0.025. \quad (16)$$

This equation was solved with the *uniroot* function and the solution obtained was $\alpha = 1.169235$. With this value of α and the assumed mean, $\beta = 0.02386193$. The complete R code can be found in the file 'Parameter calculator.R'.

Example 3: cost of colonoscopy

The mean reported was £372, the lower quartile £141 and the upper quartile £474. The multivariate methods we tried did not work for the gamma distribution. Therefore, the *uniroot* function was also used here.

In this case, the idea behind this method is to find the shape parameter such that the mean of a gamma distribution is £372 and (for example) the upper quartile of a gamma distribution is £474 (the lower quartile can also be used). The latter can be expressed in R as the following equation:

$$F1 = \text{pgamma}(474, \text{shape}, \text{scale} = \text{scale}) - 0.75. \quad (17)$$

Note also that for the gamma distribution the following equation always holds:

$$\text{scale} = \text{mean}/\text{shape}. \quad (18)$$

Thus, substitution in F1 above yields:

$$F1 = \text{pgamma}(474, \text{shape}, \text{scale} = \text{mean}/\text{shape}) - 0.75. \quad (19)$$

This equation was solved with the *uniroot* function and the solution obtained was shape = 4.126228. With this value and the mean, scale = 90.15498. The complete R code can be found in the file 'Parameter calculator.R'.

Appendix 11 Results (full incremental and intervention versus comparator) of base case and scenario analyses

TABLE 72 Lifetime results for all of the strategies in the base-case scenario (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28	NA	NA	NA
OC-Sensor	18.6239	244.42	0.0020	12.14	6133
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	274.75	–0.0003	–30.33	88,798

NA, not applicable.

TABLE 73 Lifetime results for intervention vs. comparator in the base-case scenario (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	42.47	18,296
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.14	6133
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259.25	4,133,559

TABLE 74 Lifetime results for all of the strategies in the base-case scenario (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6415	230.49	NA	NA	NA
OC-Sensor	18.6439	242.51	0.0024	12.02	5039
No triage (referral straight to colonoscopy)	18.6440	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6444	272.50	0.0005	29.99	61,619

NA, not applicable.

TABLE 75 Lifetime results for intervention vs. comparator in the base-case scenario (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0029	42.01	14,626
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0004	–228.10	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0024	12.02	5039
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–258.09	2,578,543

TABLE 76 Lifetime results for all of the strategies in the scenario that a proportion of patients receives a second FIT/gFOBT: results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.32	NA	NA	NA
OC-Sensor	18.6239	244.67	0.002	12.35	6237
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	275.05	0.0003	30.38	88,936

NA, not applicable.

TABLE 77 Lifetime results for intervention vs. comparator in the scenario that a proportion of patients receives a second FIT/gFOBT: results for all of the strategies (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	43	18,405
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–229	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12	6237
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259	4,129,585

TABLE 78 Lifetime results for all of the strategies in the scenario that a proportion of patients receives a second FIT/gFOBT: results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6403	231	NA	NA	NA
OC-Sensor	18.6427	243	0.0024	12.22	5125
No triage (referral straight to colonoscopy)	18.6428	501	Dominated by HM-JACKarc		
HM-JACKarc	18.6431	273	0.0005	30.04	61,322

NA, not applicable.

TABLE 79 Lifetime results for intervention vs. comparator in the scenario that a proportion of patients receives a second FIT/gFOBT: results for all of the strategies (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0029	42.26	14,706
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0004	–227.80	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0024	12.22	5125
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–257.84	2,533,617

TABLE 80 Lifetime results for all of the strategies in the scenario that prevalence of CRC is asymmetric (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232	NA	NA	NA
OC-Sensor	18.6239	244	0.0020	12.14	6133
No triage (referral straight to colonoscopy)	18.6239	504	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	275	0.0003	30.33	88,798

NA, not applicable.

TABLE 81 Lifetime results for intervention vs. comparator in the scenario that prevalence of CRC is asymmetric (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	42	18,296
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–229	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12	6133
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259	4,133,559

TABLE 82 Lifetime results for all of the strategies in the scenario that prevalence of CRC is asymmetric (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.4512	246.83	NA	NA	NA
OC-Sensor	18.4554	261.06	0.0042	14.24	3354
No triage (referral straight to colonoscopy)	18.4559	516.60	Dominated by HM-JACKarc		
HM-JACKarc	18.4564	291.04	0.0009	29.98	32,276

NA, not applicable.

TABLE 83 Lifetime results for all of the strategies in the scenario that prevalence of CRC is asymmetric (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0052	44.22	8545
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0005	–225.56	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0042	14.24	3354
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–255.54	601,774

TABLE 84 Lifetime results all of the strategies in the scenario in which FOB Gold is included (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28	NA	NA	NA
FOB Gold	18.6238	262.72	Dominated by OC-Sensor		
OC-Sensor	18.6239	244.42	0.0020	12.14	6133
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	274.75	0.0003	30.33	88,798

NA, not applicable.

TABLE 85 Lifetime results intervention vs. comparator in scenario in which FOB Gold is included (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	42.47	18,296
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.14	6133
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259.25	4,133,559
FOB Gold vs. gFOBT	0.0019	30.44	15,720
FOB Gold vs. no triage (referral straight to colonoscopy)	–0.0001	–240.95	2,273,829

TABLE 86 Lifetime results for all of the strategies in the scenario in which FOB Gold is included (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6424	230.92	NA	NA	NA
FOB Gold	18.6444	261.07	Dominated by OC-Sensor		
OC-Sensor	18.6444	242.92	0.0020	12.00	6081
No triage (referral straight to colonoscopy)	18.6445	500.69	Dominated by HM-JACKarc		
HM-JACKarc	18.6446	272.94	0.0002	30.02	128,618

NA, not applicable.

TABLE 87 Lifetime results for intervention vs. comparator in the scenario in which FOB Gold is included (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0022	42.02	19,040
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0001	–227.75	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.00	6081
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–257.76	2,830,605
FOB Gold vs. gFOBT	0.0020	30.14	15,456
FOB Gold vs. no triage (referral straight to colonoscopy)	–0.0001	–239.62	2,097,433

TABLE 88 Lifetime results for all of the strategies in the scenario with increased mortality due to colonoscopy (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
No triage (referral straight to colonoscopy)	18.6064	503.65	Dominated by gFOBT		
gFOBT	18.6148	232.26			
HM-JACKarc	18.6157	274.73	Dominated by OC-Sensor		
OC-Sensor	18.6165	244.40	0.0017	12.14	7144

TABLE 89 Lifetime results for intervention vs. comparator in the scenario with increased mortality due to colonoscopy: intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0009	42.47	45,271
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0093	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0017	12.14	7144
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0101	–259.25	OC-Sensor dominates

TABLE 90 Lifetime results for all of the strategies in the scenario with increased mortality due to colonoscopy (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
No triage (referral straight to colonoscopy)	18.6258	500	Dominated by gFOBT		
gFOBT	18.6343	230			
HM-JACKarc	18.6350	272	Dominated by OC-Sensor		
OC-Sensor	18.6359	243	0.0016	12.08	7535

TABLE 91 Lifetime results for intervention vs. comparator in the scenario with increased mortality due to colonoscopy (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0007	42.05	58,563
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0092	–227.77	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0016	12.08	7535
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0101	–257.74	OC-Sensor dominates

TABLE 92 Lifetime results for all of the strategies in the scenario in which the diagnosis was delayed with 1 year (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6195	230.90	NA	NA	NA
OC-Sensor	18.6235	244.20	0.0040	13.30	3352
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	274.75	0.0007	30.55	43,642

NA, not applicable.

TABLE 93 Lifetime results for intervention vs. comparator in the scenario in which the diagnosis was delayed with 1 year (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0047	43.85	9360
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0040	13.30	3352
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–259.47	592,092

TABLE 94 Lifetime results for all of the strategies in the scenario in which the diagnosis was delayed with 1 year (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6316	229.27	NA	NA	NA
OC-Sensor	18.6357	242.63	0.0040	13.37	3306
No triage (referral straight to colonoscopy)	18.6361	500.61	Dominated by HM-JACKarc		
HM-JACKarc	18.6363	272.76	0.0006	30.13	48,223

NA, not applicable.

TABLE 95 Lifetime results for intervention vs. comparator in the scenario in which the diagnosis was delayed with 1 year (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0047	43.50	9318
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0001	–227.85	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0040	13.37	3306
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0005	–257.97	539,543

TABLE 96 Lifetime results for all of the strategies in the scenario that the FIT threshold was set to ≥ 20µg Hb/g faeces (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28	NA	NA	NA
FOB Gold	18.6237	240.62	0.0018	8.34	4725
OC-Sensor	18.6238	241.83	0.0001	1.21	12,576
No triage (referral straight to colonoscopy)	18.6239	503.67	0.0002	261.84	1,449,585

NA, not applicable.

TABLE 97 Lifetime results for intervention vs. comparator in the scenario that the FIT threshold was set to ≥ 20 µg Hb/g faeces (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
FOB Gold vs. gFOBT	0.0018	8.34	4725
FOB Gold vs. no triage (referral straight to colonoscopy)	–0.0003	–263.05	950,102
OC-Sensor vs. gFOBT	0.0019	9.55	5131
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–261.84	1,449,585

TABLE 98 Lifetime results for all of the strategies in the scenario that the FIT threshold was set to ≥ 20µg Hb/g faeces (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6386	231.69	NA	NA	NA
OC-Sensor	18.6406	241.21	Dominated by FOB-Gold		
FOB Gold	18.6406	240.01	0.0019	8.33	4283
No triage (referral straight to colonoscopy)	18.6408	500.60	0.0002	260.59	1,365,199

NA, not applicable.

TABLE 99 Lifetime results for intervention vs. comparator in the scenario that the FIT threshold was set to ≥ 20µg Hb/g faeces (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
FOB Gold vs. gFOBT	0.0019	8.33	4283
FOB Gold vs. no triage (referral straight to colonoscopy)	–0.0002	–260.59	1,365,199
OC-Sensor vs. gFOBT	0.0019	9.53	4962
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–259.39	1,212,654

TABLE 100 Lifetime results for all of the strategies in the scenario for which accuracy data for faecal occult blood testing are taken from Bjerregaard *et al.*[93] (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6230	258.97	Dominated by OC-Sensor		
OC-Sensor	18.6239	244.42			
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	274.75	0.0003	30.33	88,798

TABLE 101 Lifetime results for intervention vs. comparator in the scenario for which accuracy data for faecal occult blood testing are taken from Bjerregaard *et al.*[93] (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0012	15.78	13,482
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0008	–14.55	OC-Sensor dominates
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259.25	4,133,559

TABLE 102 Lifetime results for all of the strategies in the scenario for which accuracy data for faecal occult blood testing are taken from Bjerregaard *et al.*[93] (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6432	257.38	Dominated by OC-Sensor		
OC-Sensor	18.6440	242.90			
No triage (referral straight to colonoscopy)	18.6441	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6444	272.90	0.0003	30.00	88,544

TABLE 103 Lifetime results for intervention vs. comparator in the scenario for which accuracy data for faecal occult blood testing are taken from Bjerregaard *et al.*[93] (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0012	15.52	13,019
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–227.70	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0009	–14.48	OC-Sensor dominates
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–257.70	3,119,555

TABLE 104 Lifetime results for all of the strategies in the scenario for which accuracy data for faecal occult blood testing are taken from Niv and Sperber[92] (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6227	277.55	Dominated by OC-Sensor		
OC-Sensor	18.6239	244.42			
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	274.75	0.0003	30.33	88,798

TABLE 105 Lifetime results for intervention vs. comparator in the scenario for which accuracy data for faecal occult blood testing are taken from Niv and Sperber[92] (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0015	–3	HM-JACKarc dominates
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–229	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0011	–33	OC-Sensor dominates
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–259	4,133,559

TABLE 106 Lifetime results for all of the strategies in the scenario for which accuracy data for faecal occult blood testing are taken from Niv and Sperber[92] (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6425	275.67	Dominated by OC-Sensor		
OC-Sensor	18.6436	242.63			
No triage (referral straight to colonoscopy)	18.6436	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6439	272.69	0.0004	30.05	83,261

TABLE 107 Lifetime results for intervention vs. comparator in the scenario for which accuracy data for faecal occult blood testing are taken from Niv and Sperber[92] (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0014	–2.99	HM-JACKarc dominates
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–227.91	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0010	–33.04	OC-Sensor dominates
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–257.96	3,117,361

TABLE 108 Lifetime results for all of the strategies in the scenario for which the distribution of the Dukes' stages is based on Cubiella *et al.*[55] (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6215	232.02	NA	NA	NA
No triage (referral straight to colonoscopy)	18.6231	503.16	Dominated by OC-Sensor		
OC-Sensor	18.6231	243.95	0.0016	11.93	7454
HM-JACKarc	18.6234	274.24	0.0003	30.29	110,838

NA, not applicable.

TABLE 109 Lifetime results for intervention vs. comparator in the scenario for which the distribution of the Dukes' stages is based on Cubiella *et al.*[55] (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0019	42	22,319
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–229	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0016	12	7370
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0000	–259	OC-Sensor dominates

TABLE 110 Lifetime results for all of the strategies in the scenario for which the distribution of the Dukes' stages is based on Cubiella *et al.*[55] (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
OC-Sensor	18.6355	242.48	0.0018	11.94	6499
No triage (referral straight to colonoscopy)	18.6355	500.11	Dominated by HM-JACKarc		
HM-JACKarc	18.6357	272.41	0.0002	29.93	183,714
OC-Sensor	18.6355	242.48	0.0018	11.94	6499

TABLE 111 Lifetime results for intervention vs. comparator in the scenario for which the distribution of the Dukes' stages is based on Cubiella *et al.*[55] (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0020	41.88	20,934
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0002	–227.70	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0018	11.94	6499
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0000	–257.64	64,414,134

TABLE 112 Lifetime results for all of the strategies in the scenario for which the distribution of the Dukes' stages is based on expert opinion (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6227	232.71	NA	NA	NA
OC-Sensor	18.6254	245.21	0.0027	12.50	4655
No triage (referral straight to colonoscopy)	18.6256	504.53	Dominated by HM-JACKarc		
HM-JACKarc	18.6259	275.61	0.0005	30.40	60,798

NA, not applicable.

TABLE 113 Lifetime results for all intervention vs. comparator in the scenario for which the distribution of the Dukes' stages is based on expert opinion (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0032	42.90	13,574
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0027	12.50	OC-Sensor dominates
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–259.32	1,322,872

TABLE 114 Lifetime results for all of the strategies in the scenario for which the distribution of the Dukes' stages is based on expert opinion (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6424	230.92	NA	NA	NA
OC-Sensor	18.6455	243.30	0.0031	12.38	3984
No triage (referral straight to colonoscopy)	18.6457	501.46	Dominated by HM-JACKarc		
HM-JACKarc	18.6461	273.34	0.0006	30.04	50,961

NA, not applicable.

TABLE 115 Lifetime results for intervention vs. comparator in the scenario for which the distribution of the Dukes' stages is based on expert opinion (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0037	42.42	11,476
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0004	–228.12	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0031	12.38	3984
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–258.16	1,081,160

TABLE 116 Lifetime results: scenario with no adverse events associated to colonoscopy – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6221	230.97			
OC-Sensor	18.6241	243.06	0.002	12.09	6081
No triage (referral straight to colonoscopy)	18.6245	500.49	Dominated by HM-JACKarc		
HM-JACKarc	18.6245	273.19	0.0004	30.13	80,244

TABLE 117 Lifetime results: scenario with no adverse events associated to colonoscopy – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0024	42.23	17,862
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0000	–227.30	Dominated by HM-JACKarc
OC-Sensor vs. gFOBT	0.0020	12.09	6081
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–257.43	685,532

TABLE 118 Lifetime results: scenario with no adverse events associated to colonoscopy – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6431	229.66			
OC-Sensor	18.6453	241.61	0.0022	11.96	5406
HM-JACKarc	18.6457	271.48	0.0004	29.87	81,573
No triage (referral straight to colonoscopy)	18.6457	497.00	0.0000	225.52	9,135,836

TABLE 119 Lifetime results: scenario with no adverse events associated to colonoscopy – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0026	41.82	16,224.64
HM-JACKarc vs. no triage (referral straight to colonoscopy)	–0.00002	–225.52	9,135,836.87
OC-Sensor vs. gFOBT	0.0022	11.96	5406.14
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–255.39	653,493.58

TABLE 120 Lifetime results: scenario without CRC progression – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.701	263.92			
OC-Sensor	18.711	279.10	0.0101	15.18	1508
No triage (referral straight to colonoscopy)	18.713	538.93	Dominated by HM-JACKarc		
HM-JACKarc	18.713	310.01	0.0019	30.9054	16,528

TABLE 121 Lifetime results: scenario without CRC progression – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0119	46.09	3859
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–228.92	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0101	15.18	1508
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0016	–259.83	163,305

TABLE 122 Lifetime results: scenario without CRC progression – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.7191	262.22			
OC-Sensor	18.7291	277.18	0.0101	14.96	1485
HM-JACKarc	18.7307	307.57	0.0015	30.39	19,790
No triage (referral straight to colonoscopy)	18.7307	535.84	0.0001	228.27	4,171,882

TABLE 123 Lifetime results: scenario without CRC progression: intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0116	45.36	3907
HM-JACKarc vs. no triage (referral straight to colonoscopy)	–0.0001	–228.27	4,171,882
OC-Sensor vs. gFOBT	0.0101	14.96	1485
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0016	–258.66	162,620

TABLE 124 Lifetime results: scenario for which all patients referred to colonoscopy as opposed to CTC – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	243.73			
OC-Sensor	18.6239	256.31	0.002	12.58	6352
No triage (referral straight to colonoscopy)	18.6239	531.40	Dominated by HM-JACKarc		
HM-JACKarc	18.6242	288.36	0.0003	32.05	93,832

TABLE 125 Lifetime results: scenario for which all patients referred to colonoscopy as opposed to CTC – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	44.63	19,224
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–243.05	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.58	6352
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–275.10	4,386,188

TABLE 126 Lifetime results: scenario all patients referred to colonoscopy as opposed to CTC – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6390	243.13			
OC-Sensor	18.6410	255.60	0.0020	12.46	6158
No triage (referral straight to colonoscopy)	18.6411	527.98	Dominated by HM-JACKarc		
HM-JACKarc	18.6412	286.99	0.00	31.39	156,950

TABLE 127 Lifetime results: scenario all patients referred to colonoscopy as opposed to CTC – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	43.86	19,406
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–243.05	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	12.46	6159
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–272.39	3,859,404

TABLE 128 Lifetime results: scenario for OC threshold – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6219	232.28			
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by OC-Sensor		
OC-Sensor	18.6241	375.40	0.0022	143.12	65,055

TABLE 129 Lifetime results: scenario for OC threshold – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
OC-Sensor vs. gFOBT	0.0022	143.12	65,191.91
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0002	–128.27	OC-Sensor dominates

TABLE 130 Lifetime results: scenario for OC threshold – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6384	232.10			
No triage (referral straight to colonoscopy)	18.6404	500.63	Dominated by OC-Sensor		
OC-Sensor	18.6406	373.75	0.0022	141.65	64,386

TABLE 131 Lifetime results: scenario for OC threshold – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
OC-Sensor vs. gFOBT	0.0022	141.65	65,696
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.0002	–126.88	OC-Sensor dominates

TABLE 132 Lifetime results: scenario double probability of persisting in symptoms after negative test result – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6217	381.09			
OC-Sensor	18.6237	389.26	0.002	8.17	4118
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by HM-JACKarc		
HM-JACKarc	18.6241	403.87	0.0004	14.61	36,534

TABLE 133 Lifetime results: scenario double probability of persisting in symptoms after negative test result – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	22.78	9729
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0001	–99.80	Dominated by HM-JACKarc
OC-Sensor vs. gFOBT	0.0020	8.17	4118
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–114.42	536,359

TABLE 134 Lifetime results: scenario double probability of persisting in symptoms after negative test result – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6416	379.39			
OC-Sensor	18.6437	387.44	0.0021	8.05	3793
No triage (referral straight to colonoscopy)	18.6439	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6440	401.82	0.0003	14.38	47,933

TABLE 135 Lifetime results: scenario double probability of persisting in symptoms after negative test result – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0024	22.43	9421
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0000	–98.78	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0021	8.05	3794
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0002	–113.16	508,628

TABLE 136 Lifetime results: scenario half probability of persisting in symptoms after negative test result – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6220	157.88			
No triage (referral straight to colonoscopy)	18.6239	503.67	Dominated by OC-Sensor		
OC-Sensor	18.6239	172.01	0.002	14.13	7143
HM-JACKarc	18.6243	210.19	0.0003	38.19	114,546

TABLE 137 Lifetime results: scenario half probability of persisting in symptoms after negative test result – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0023	52.32	22,637
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–293.48	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0020	14.13	7143
OC-Sensor vs. no triage (referral straight to colonoscopy)	0.00001	–331.67	OC-Sensor dominates

TABLE 138 Lifetime results: scenario half probability of persisting in symptoms after negative test result – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.6427	156.42			
OC-Sensor	18.6445	170.45	0.0018	14.04	7697
No triage (referral straight to colonoscopy)	18.6446	500.60	Dominated by HM-JACKarc		
HM-JACKarc	18.6449	208.24	0.0004	37.79	94,475

TABLE 139 Lifetime results: scenario half probability of persisting in symptoms after negative test result – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0022	51.82	23,340
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–292.36	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0018	14.04	7697
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0001	–330.15	5,370,520

TABLE 140 Lifetime results: prevalence 3% – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.3672	253.88			
OC-Sensor	18.3712	269.06	0.0040	15.19	3829
No triage (referral straight to colonoscopy)	18.3716	524.89	Dominated by HM-JACKarc		
HM-JACKarc	18.3719	299.55	0.0007	30.49	42,517

TABLE 141 Lifetime results: prevalence 3% – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0047	45.68	9754
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–225.34	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.004	15.19	3829
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0004	–255.83	578,092

TABLE 142 Lifetime results: prevalence 3% – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	18.3886	252.18			
OC-Sensor	18.3934	267.17	0.0048	14.99	3137
No triage (referral straight to colonoscopy)	18.3939	521.86	Dominated by HM-JACKarc		
HM-JACKarc	18.3944	297.15	0.001	30	29,980

TABLE 143 Lifetime results: prevalence 3% – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0058	44.97	7773
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0005	–224.71	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0048	14.99	3137
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0005	–254.69	491,877

TABLE 144 Lifetime results: prevalence 5.4% – results for all of the strategies (deterministic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	17.9597	288.43			
OC-Sensor	17.9668	308.48	0.0071	20.06	2808
No triage (referral straight to colonoscopy)	17.9679	558.85	Dominated by HM-JACKarc		
HM-JACKarc	17.9681	339.23	0.0013	30.75	23,327

TABLE 145 Lifetime results: prevalence 5.4% – intervention vs. comparator (deterministic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0085	50.80	6004
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0003	–219.62	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0071	20.06	2808
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0011	–250.36	238,380

TABLE 146 Lifetime results: prevalence 5.4% – results for all of the strategies (probabilistic)

	QALYs	Cost (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
gFOBT	17.9840	286.88			
OC-Sensor	17.9926	306.63	0.0086	19.75	2304
No triage (referral straight to colonoscopy)	17.9937	555.87	Dominated by HM-JACKarc		
HM-JACKarc	17.9943	336.60	0.0017	29.97	17,629

TABLE 147 Lifetime results: prevalence 5.4% – intervention vs. comparator (probabilistic)

	Incremental QALYs	Incremental cost (£)	ICER (£)
HM-JACKarc vs. gFOBT	0.0104	49.72	4798
HM-JACKarc vs. no triage (referral straight to colonoscopy)	0.0006	–219.28	HM-JACKarc dominates
OC-Sensor vs. gFOBT	0.0086	19.75	2304
OC-Sensor vs. no triage (referral straight to colonoscopy)	–0.0012	–249.25	210,923

Appendix 12 National Institute for Health and Care Excellence guidance relevant to colorectal cancer

Published National Institute for Health and Care Excellence guidance

Aflibercept in Combination with Irinotecan and Fluorouracil-based Therapy for Treating Metastatic Colorectal Cancer that has Progressed Following Prior Oxaliplatin-based Chemotherapy. NICE technology appraisal guidance TA307; March 2014. URL: www.nice.org.uk/guidance/ta307 (accessed 9 August 2016).

Bevacizumab and Cetuximab for the Treatment of Metastatic Colorectal Cancer. NICE technology appraisal guidance TA118; January 2007. URL: www.nice.org.uk/guidance/ta118 (accessed 9 August 2016).

Bevacizumab in Combination with Oxaliplatin and either Fluorouracil plus Folinic Acid or Capecitabine for the Treatment of Metastatic Colorectal Cancer. NICE technology appraisal guidance TA212; December 2010. URL: www.nice.org.uk/guidance/ta212 (accessed 9 August 2016).

Capecitabine and Oxaliplatin in the Adjuvant Treatment of Stage III (Dukes's C) Colon Cancer. NICE technology appraisal guidance TA100; April 2006. URL: www.nice.org.uk/guidance/ta100 (accessed 9 August 2016).

Cetuximab and Panitumumab for Previously Untreated Metastatic Colorectal Cancer. NICE technology appraisal guidance TA439; March 2017. URL: www.nice.org.uk/guidance/ta439 (accessed 9 August 2016).

Cetuximab for the First-line Treatment of Metastatic Colorectal Cancer. NICE technology appraisal guidance TA176; August 2009. URL: www.nice.org.uk/guidance/ta176 (accessed 9 August 2016).

Cetuximab, Bevacizumab and Panitumumab for the Treatment of Metastatic Colorectal Cancer after First-line Chemotherapy: Cetuximab (monotherapy or combination chemotherapy), Bevacizumab (in combination with non-oxaliplatin chemotherapy) and Panitumumab (monotherapy) for the Treatment of Metastatic Colorectal Cancer after first-line Chemotherapy. Review of technology appraisal guidance TA150 and part review of technology appraisal guidance TA118. NICE technology appraisal guidance TA242; January 2012. URL: www.nice.org.uk/guidance/ta242 (accessed 9 August 2016).

Colorectal Cancer Prevention: Colonoscopic Surveillance in Adults with Ulcerative Colitis, Crohn's Disease or Adenomas. NICE clinical guideline CG118; March 2011. URL: www.nice.org.uk/guidance/cg118 (accessed 9 August 2016). Date for review: February 2019.

Colorectal Cancer: Diagnosis and Management. NICE clinical guideline CG131; November 2011, updated December 2014. URL: www.nice.org.uk/guidance/cg131 (accessed 9 August 2016). Date for review: February 2016.

Combined Endoscopic and Laparoscopic Removal of Colonic Polyps. NICE interventional procedure guidance IPG503; September 2014. URL: www.nice.org.uk/guidance/ipg503 (accessed 9 August 2016).

Computed Tomographic Colonography (Virtual Colonoscopy). NICE interventional procedure guidance IPG129; June 2005. URL: www.nice.org.uk/guidance/ipg129 (accessed 9 August 2016).

Cytoreduction Surgery followed by Hyperthermic Intraoperative Peritoneal Chemotherapy for Peritoneal Carcinomatosis. NICE interventional procedure guidance IPG331; February 2010. URL: www.nice.org.uk/guidance/ipg331 (accessed 9 August 2016).

Endoscopic Submucosal Dissection of Lower Gastrointestinal Lesions. NICE interventional procedure guidance IPG335; March 2010. URL: www.nice.org.uk/guidance/ipg335 (accessed 9 August 2016).

Fluorouracil chemotherapy: The My5-FU Assay for Guiding Dose Adjustment. NICE diagnostic guidance DG16; December 2014. URL: www.nice.org.uk/guidance/dg16 (accessed 9 August 2016).

Guidance on the Use of Capecitabine and Tegafur with Uracil for Metastatic Colorectal Cancer. NICE technology appraisal guidance TA61; May 2003. URL: www.nice.org.uk/guidance/ta61 (accessed 9 August 2016).

Improving Outcomes in Colorectal Cancer. NICE guidance on cancer services CSG5; June 2004. URL: www.nice.org.uk/guidance/csg5 (accessed 9 August 2016). To be updated by the update of the guideline on colorectal cancer (NICE guideline CG131).

Laparoscopic Surgery for Colorectal Cancer. NICE technology appraisal guidance TA105; August 2006. URL: www.nice.org.uk/guidance/ta105 (accessed 9 August 2016).

Preoperative High Dose Rate Brachytherapy for Rectal Cancer. NICE interventional procedure guidance IPG531; August 2015. URL: www.nice.org.uk/guidance/ipg531 (accessed 9 August 2016).

Radiofrequency Ablation for Colorectal Liver Metastases. NICE interventional procedure guidance IPG327; December 2009. URL: www.nice.org.uk/guidance/ipg327 (accessed 9 August 2016).

Selective Internal Radiation Therapy for Non-resectable Colorectal Metastases in the Liver. NICE interventional procedure guidance IPG401; July 2011, updated May 2013. URL: www.nice.org.uk/guidance/ipg401 (accessed 9 August 2016).

Suspected Cancer: Recognition and Referral. NICE guideline NG12; June 2015. URL: www.nice.org.uk/guidance/ng12 (accessed 9 August 2016).

Transanal Total Mesorectal Excision of the Rectum. NICE interventional procedure guidance IPG514; March 2015. URL: www.nice.org.uk/guidance/ipg514 (accessed 9 August 2016).

Wireless Capsule Endoscopy for Investigation of the Small Bowel. NICE interventional procedure guidance IPG101; 2004. URL: www.nice.org.uk/guidance/ipg101 (accessed 9 August 2016).

National Institute for Health and Care Excellence guidance under development

Colon Cancer (adjuvant) – Irinotecan [ID379]. NICE technology appraisal guidance. URL: www.nice.org.uk/guidance/indevelopment/gid-tag380 (accessed 9 August 2016). Expected publication date: TBC.

Low-energy Contact X-ray Brachytherapy (the Papillon Technique) for Early-stage Rectal Cancer. NICE interventional procedure guidance IPG532; September 2015. URL: www.nice.org.uk/guidance/indevelopment/gid-ip1234 (accessed 9 August 2016).

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