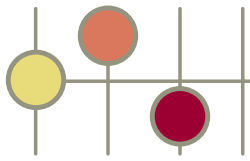

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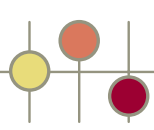
Diagnostic Accuracy and Cost-Effectiveness of Faecal Occult Blood Tests Used in Screening for Colorectal Cancer: A Systematic Review



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REPORT 36

DIAGNOSTIC ACCURACY AND COST-EFFECTIVENESS OF FAECAL OCCULT BLOOD TESTS (FOBT) USED IN SCREENING FOR COLORECTAL CANCER: A SYSTEMATIC REVIEW

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LIST OF ABBREVIATIONS

CBA	Cost benefit analysis
CCT	Case-controls study
CEA	Cost-effectiveness analysis
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CUA	Cost-utility analysis
DALY	Disability adjusted life years
DC	Diagnostic cohort
DCC	Diagnostic case-control
DOR	Diagnostic odds ratio
FDA	Food and Drug Administration
FOBT	Faecal occult blood test
gFOBT	Guaiac FOBT
GHQ	General Health Questionnaire
HO (HO II)	Haemoccult (Haemoccult)
HS	Haemoccult Sensa
iFOBT	Immunochemical FOBT
IT	Index test
-LR	Negative likelihood ratio
-veFOBT	Patients with a negative FOBT
NHS EED	NHS Economic Evaluation Database
NPV	Negative predictive value
95% CI	95% Confidence interval
PPV	Positive predictive value
+LR	Positive likelihood ratio
+veFOBT	Patients with a positive FOBT
QALY	Quality Adjusted Life Year
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomised controlled trial
ROC	Receiver operating curve
RPHA	Reverse passive haemagglutination
RS	Reference standard
sROC	Summary receiver operating curve
STARD	Standards for Reporting of Diagnostic Accuracy
UK	United Kingdom
UK Pilot	UK Colorectal Cancer Screening Pilot
USA	United States of America

MEASURES OF DIAGNOSTIC TEST PERFORMANCE

This section summarises the measures of diagnostic test performance used in the review, and how these are calculated.

		Reference Standard	
		+	**-**
Test result	**+**	a	b
	-	c	d

True positives (TP)	Number of people correctly diagnosed as having the disease (a)
True negatives (TN)	Number of people correctly diagnosed as not having the disease (d)
False positives (FP)	Number of people with a positive test result that do not have the disease (b)
False negatives (FN)	Number of people with a negative test result that have the disease (c)
Sensitivity	a/(a + c) – Proportion of people with the target disorder who have a positive test result.
Specificity	d/(b + d) - Proportion of people without the target disorder who have a negative test result.
Test accuracy	Proportion of people that were correctly identified as having the disease, or not having the disease (a+d / a+b+c+d)
Likelihood ratio (LR) : **positive (+ LR)** **negative (-LR)**	Describes how many times a person with disease is more likely to receive a particular test result than a person without disease. A likelihood ratio of a positive test result is usually a number greater than 1, a likelihood ratio of a negative test result usually lies between 0 and 1. + LR=[a/(a + c)] / [b/(b + d)] = sensitivity / (1 –specificity) - LR = [c/(a + c)] / [d/(b + d)] = (1 – sensitivity) / specificity
Diagnostic odds ratio (DOR)	Used as an overall (single indicator) measure of the diagnostic accuracy of a test. It is calculated as the odds of positivity among diseased people, divided by the odds of positivity among non-diseased people. When a test provides no diagnostic evidence then the DOR is 1.0. [sensitivity/(1–specificity)] / [(1–sensitivity)/ specificity] + LR / -LR ad/bc
Positive predictive value (PPV)	The probability of disease among all persons with a positive test result: a/(a + b)

Negative predictive value (NPV)

The probability of non-disease among all persons with a negative test result: d/(c + d)

Receiver operating curve (ROC curve)

A ROC curve represents the relationship between 'true positive fraction' (sensitivity) and 'false positive fraction' (1 – specificity). It displays the trade-offs between sensitivity and specificity as a result of varying the cut-off value for positivity in case of a continuous test result.

Summary ROC curve (sROC curve)

The summary ROC approach models test accuracy, defined by the log of the diagnostic odds ratio (D=logit(sensitivity) - logit(1-specificity)), as a function of test threshold (S= logit(sensitivity) + logit(1-specificity)). S relates to the positivity threshold: it has a value of 0 in studies where sensitivity equals specificity, it is positive in studies where sensitivity is higher than specificity, and negative when specificity is higher than sensitivity. For a set of primary studies, the following linear regression model is fitted:

$D=\alpha+\beta S$

where D is the log odds ratio in each study, α is the intercept, which is the expected log odds ratio when S=0, β is the coefficient of S, indicating whether the log diagnostic odds ratio varies with the threshold.

The estimated summary ROC-curve can be plotted by computing the expected sensitivity for each value of 1-specificity across the range of the observed values. The expected sensitivity is given by:
$sensitivity=[1+e^{-\alpha(1-\beta)}.V^{(1+\beta)(1-\beta)}]^{-1}$
where V=specificity/(1-specificity)

EXECUTIVE SUMMARY

Background

Early detection and removal of carcinomas and precancerous adenomas can reduce mortality from colorectal cancer (CRC). FOBTs utilise the fact that CRC and large polyps tend to bleed. Guaiac FOBTs detect the haem moiety of haemoglobin molecules by making use of the pseudoperoxidase activity of haem. Haem releases oxygen from hydrogen peroxide (the developer), which then reacts with the colourless guaiac to form a blue dye. Immunochemical FOBTs are said to be more sensitive because they use monoclonal or polyclonal antibodies raised against the globin moiety of human haemoglobin, detecting intact human haemoglobin or its very early degradation products. Screening using FOBTs has been shown in clinical trials to reduce mortality from CRC by 15 to 33%, for average risk populations. During 2000-2002, the UK CRC Screening Pilot was carried out in order to determine the feasibility of screening for CRC in the UK population using the guaiac FOBT, Hema-Screen, and to verify whether mortality reductions achieved in the setting of randomised trials could be repeated in population based programmes. The results led the National Screening Committee to recommend FOBTs as the initial method for CRC screening of an average risk population. However, due to the "need for repeatedly testing 'weak positive' results", further research into the possible use of an immunochemical FOBTs was recommended.

Objectives

This review aimed to determine the diagnostic accuracy and cost effectiveness of different types of FOBT, for screening for adenomas and/or CRC in an average risk population, with a view to determining whether a specific FOBT could be singled out as the most accurate and cost-effective.

Methods

A systematic review was undertaken according to the Centre for Reviews and Dissemination guidelines for undertaking systematic reviews.[11]

Data sources: studies were identified through searches of electronic databases, internet searches, hand-searching of relevant journals, scanning reference lists of included studies and reviews, and consultation with experts in the field.

Study selection: Two reviewers screened titles and abstracts for relevance. Full papers of potentially relevant studies were assessed for inclusion by one reviewer with random checking by a second. Published and unpublished studies in any language were eligible for inclusion. Studies evaluating the diagnostic accuracy of guaiac or immunochemical FOBTs for the identification of CRC or adenomatous polyps in an average risk adult population, that reported sufficient information to construct a 2 x 2 table, were eligible for inclusion. Cohorts were also derived from randomised controlled trials comparing the efficacy of screening, using results for the intervention arm (screened population), as long as the drop out rate was less than 15%. Full economic evaluations were included if they compared at least two FOBTs and the measure of health benefit included detection of cancer and/or adenomas, or years of life saved.

Data extraction: Data extraction was performed by one reviewer and checked by a second. Quality assessment was performed independently by two reviewers.

Data synthesis: Results were analysed according to test type (immunochemical or guaiac). Within these groups, data were analysed according to target condition. For each test the ranges in sensitivity, specificity, likelihood ratios (positive and negative), and diagnostic odds ratios were calculated. Results were presented graphically as forest plots and ROC plots. Heterogeneity was investigated using the Q and I^2 statistics, and visual examination of forest plots. Where sufficient data were available, heterogeneity was further investigated using regression analysis. Due to the statistically significant heterogeneity between studies in all groups, pooling was not undertaken. A structured abstract was written for each included economic evaluation and a summary of the evaluations presented.

Results

Diagnostic accuracy of guaiac FOBTs:

- Overall, the sensitivities of guaiac FOBTs reported in diagnostic cohort studies for the detection of all neoplasms was low, ranging from approximately 6% to 46% for Haemoccult, 43% for Haemoccult Sensa, and 83% for KryptoHaem (this single study used sigmoidoscopy as the reference standard which may overestimate the accuracy of KryptoHaem).
- Generally, accuracy seemed better for the diagnosis of CRC, with sensitivities ranging from approximately 25% to 96% for Haemoccult, 62% to 79% for Haemoccult Sensa, and 27% for Shionogi B.
- The accuracy for detecting adenomas was lower, with sensitivities for Haemoccult ranging from approximately 4% to 19% for the detection of all adenomas, and 4% to 33% for the detection of adenomas of 1cm or larger.
- Specificity was 80% or higher for all tests on all measured outcomes.
- Diagnostic case control studies generally reported higher sensitivities than the cohort studies.

Diagnostic accuracy of immunochemical FOBTs:

- Overall, studies of immunochemical FOBTs had more methodological flaws than guaiac studies. Fifty-one percent were diagnostic case-control studies, and most were poorly reported.
- Overall, the sensitivities of immunochemical FOBTs reported in diagnostic cohort studies for the detection of all neoplasms varied between approximately 5% (OC Light) and 63% (Immudia HemSp).
- For the diagnosis of CRC, sensitivities ranged from approximately 2% (Flexsure) to 98% (MonoHaem), for all adenomas from 4% (OC Light) to 63% (Immudia HemSp), and for adenomas of 1cm or larger from 28% (Flexsure) to 67% (Immudia HemSp).
- Specificity was 89% or higher for all named immunochemical FOBTs on all measured outcomes.
- Where a test was evaluated in both cohort and case-control studies, the case control studies reported higher sensitivities than the cohort studies.

Comparison of immunochemical and guaiac FOBTs: Direct comparisons between guaiac and immunochemical FOBTs were few and gave inconsistent, and often conflicting, results. Less reliable indirect comparisons showed no clear preference for either guaiac or immunochemical FOBTs.

Economic evaluations: Seven full economic evaluations were included. Studies varied in relation to outcomes reported, the perspective taken, sensitivities and specificities used as thresholds, the stage of disease being detected and the age range of the screening cohorts. In addition, the range of countries in which the studies were conducted, and their year of publication, means that generalisability of the results of the evaluations is uncertain.

Conclusions

Studies that included direct comparisons indicated a better overall test performance for immunochemical than for guaiac FOBTs, but this evidence was very limited and of poor quality. Indirect comparisons showed no clear evidence to suggest that either guaiac or immunochemical FOBTs performed better. Poor reporting of data limited the scope of this review. We would encourage investigators to use the STARD guidelines when reporting diagnostic accuracy studies.

Implications for practice

There are data to suggest that Immudia HemSp may be superior to other immunochemical FOBTs evaluated, in terms of diagnostic accuracy. In comparison, there is little evidence that any particular guaiac FOBT has superior performance to the others. Direct comparisons between guaiac and immunochemical FOBTs gave inconsistent, and often conflicting results, therefore there is no clear evidence to suggest that either guaiac or immunochemical FOBTs have superior diagnostic accuracy, either for the detection of all neoplasms or CRC. Less reliable indirect comparisons failed to identify a clear preference for either guaiac or immunochemical FOBTs. Factors, other than accuracy, that should be considered when deciding which FOBT to use for screening include: the effects of sampling

methods and dietary restrictions upon compliance; sample storage and transportation issues, and cost-effectiveness. Data included in the review provided no clear evidence on any of these factors.

Implications for future research

Further research is required to fully evaluate the comparative diagnostic accuracy of FOBTs. Large, well designed diagnostic cohort studies, recruiting appropriate patient spectra, are required. Such studies should give consideration to the clinical information available to those interpreting tests, and this should be representative of what would be available during an actual screening programme. Consideration should be given to the use of the same reference standard to confirm diagnosis, regardless of the FOBT result. At a minimum an appropriate, standard follow-up period for participants with a negative FOBT should be defined.

Research should primarily concentrate on direct comparisons between guaiac and immunochemical FOBTs, and the relative cost-effectiveness of these tests in the UK setting. The impact of dietary restrictions and re-hydration on guaiac FOBTs also remains an area where further research would be beneficial. These practical factors, if they prove important for diagnostic accuracy, may be significant considerations when deciding whether or not to use a guaiac FOBT. Issues of patient acceptability and compliance also require further investigation. The reporting of future diagnostic accuracy studies should follow the recommendations of the STARD statement.

1. BACKGROUND

1.1 Burden of disease

Colorectal cancer (CRC) is a major health concern and a leading cause of death in the Western World. The estimated lifetime risk is 5% to 6%, with approximately 75% of new cases occurring after the age of 50.[12] In a recent report, the World Health Organization estimated a worldwide incidence of nearly 1 million cases of CRC per year.[12] Almost 50% of CRC patients will eventually die of their disease. [13]

In England and Wales over 30,000 new cases of CRC are diagnosed each year, and about half of these people will die from their disease.[14-16] The incidence of CRC is gradually increasing, largely due to the aging of the population (the rate among people aged 75 or over is ten times higher than the rate in people aged 45-55).[17] Approximately 50% of cases of CRC in the UK present in people between the ages of 50 and 69 years, and less than 1% present in people under the age of 40 years.[18]

1.2 The case for screening for colorectal cancer

Mortality from CRC can be reduced by early detection and removal of colorectal adenomas, from which approximately 95% of cancers arise.[19] Large randomised controlled trials (RCTs) have shown that annual or biennial screening for CRC neoplasms in asymptomatic people over the age of 50 years, using FOBTs, can reduce the incidence of CRC mortality by between 15 and 33%.[20-23] However, FOBT screening has also been associated with potentially harmful effects, including the complications of colonoscopy,[24] disruption of lifestyle, stress, and discomfort during screening procedures.[21, 25]

FOBT is currently the method for the initial screening of an average risk population for CRC recommended by the National Screening Committee. The choice of FOBT was based on the findings of two cancer screening workshops hosted by The Scottish and Welsh Offices and held in Edinburgh in 1997 and Cardiff in 1998. The first workshop debated the available evidence for a population screening programme for CRC and the second workshop concentrated on the practicalities of putting the theory into practice (details are available on the National Screening Committee website (http://www.open.gov.uk/doh/nsc/nsch.htm).

In order to determine the feasibility of screening for CRC in the UK population, using FOBT, and to verify whether mortality reductions achieved in the setting of RCTs could be repeated in population based programmes, pilot screening studies were carried out.[18, 26] The pilots were conducted in two sites, one in central England and the other in Scotland, during the years 2000 to 2002.[18, 26, 27]

The UK Pilot was designed as a biennial screening programme using a non-hydrated guaiac FOBT (Hema-Screen), applied without pre-test dietry restriction, in those aged between 50 and 69 years. Participants received an invitation by mail together with the test kit. Tests were performed at home on specimens collected from three consecutive bowel motions and returned by mail to one of two laboratories (located within each pilot area) for evaluation.[27] The invitation to participate and the test card were sent directly to individuals, without intervention by a clinician.

The results of the UK Pilot suggest that population based FOBT screening is feasible. The Pilot was able to reproduce the key findings from the Nottingham trial, specifically: It achieved an overall response rate close to 60%, as well as similar values for test positivity, rates of cancers detected, stage of screen-detected cancers, and the predictive value of positive tests to those observed in the trial.[26, 28] Based on international comparisons, adverse effects of screening in the UK Pilot (including complications from colonoscopy) were low. These results led to the conclusion that a national programme of FOBT screening, based on the model of screening used in the UK Pilot, should result in mortality reductions similar to those observed in the RCTs.

Because of the limited resources available, it was decided that any national CRC screening programme should concentrate on participants aged between 50 and 69 years in the first instance, with the aim of reviewing this policy after two completed rounds of screening.[18] The lower age limit was based on the fact that the incidence of CRC is very low in people under the age of 50 years.[29]

The selection of the upper age limit was based primarily on the findings of the Nottingham FOBT trial, which found that uptake of screening was low among people aged over 70 years (48%).[28]

One of the main concerns arising from the UK Pilot was the need for repeat-testing of 'weak positive' results to verify positivity. This caused the screening process to be lengthened in many cases. Further research was therefore recomended on alternative FOBT methods (e.g. immunological) with the potential to provide more definitive results on the first test.[26] Based on this recommendation, the current review aimed to assess which of the available FOBTs perform best (singly or in combination) in an average risk population invited for screening for adenomas and colorectal cancer. Alternative faecal markers are currently being developed (e.g. mutated DNA, albumin, calprotectin), but these are still in the early phases of research, and are therefore not considered in this review.[12]

1.3 The use of FOBTs in average risk population screening for CRC

FOBTs utilise the fact that CRC and large polyps tend to bleed. The test detects non-visible (occult) blood in the faeces, before there is any clinical evidence of bleeding. However, FOBTs test for the presence of blood and blood breakdown products, not neoplasia, and the presence of blood and blood breakdown products may have other causes. They are therefore used to screen average-risk asymptomatic populations in order to identify those at increased risk of having colorectal neoplasm, in whom more invasive and more accurate diagnostic tests (e.g., colonoscopy) are justified.[12, 30]

A variety of FOBTs are available including, guaiac, immunochemical, haem-porphyrin tests and flushable tests. Haem-porphyrin tests require fluorescent spectrophotometry and more complex laboratory procedures, which ultimately limit their application in a population screening setting and are therefore not considered in this review.[30, 31] Flushable FOBTs, which are interpreted by screening participants themselves and then flushed down the toilet, have not yet been evaluated in RCTs,[18] and as a health professional is not involved in reading this type of test, they will not be used by the National Screening Programme (where the test will be processed in a controlled manner). They are therefore not included in the current review. Further stool markers are currently being developed, e.g. detection of mutated DNA, tests for albumin, and calprotectin, but these are still in the early phases of research, and are therefore not considered in this review.[12]

In summary, this review considered the use of guaiac and immunochemical FOBT methodologies. FOB testing kits, for these two methods, consist of a sample collection device (usually a card, tube or wipe) and analysis based on the guaiac-peroxidase reaction or on an immunological detection system.[31] The majority of kits involve the patient collecting the stool sample and delivering the sampling device to the doctor or laboratory for analysis. Guaiac tests generally use card collection devices because drying the stool smears helps to preserve the haem moiety. Immunological methods most often use collection devices containing liquid with suitable preservatives for stool sample collection.[31]

As well as sample stability, the accuracy of FOBTs depends upon appropriate performance and interpretation of the test(s). Interpretation of FOBTs might be problematic when they are used by inexperienced personnel. In a retrospective review of questionnaires applied to accredited laboratory personnel (in order to determine their ability to interpret FOBT results), 12% were unable to correctly interpret sample test cards (mainly false-positive results).[32] This finding raised concerns that people with detectable colorectal cancers are being missed, solely because of errors in interpretation.[32-34] One suggestion to improve test interpretation is the use of tests with automated reading, such as Magstream HemSp.[35] Alternatively a centralised location for the collection, processing, and interpretation of all tests would facilitate measures to improve consistency.[32, 33]

1.3.1 Guaiac FOBTs

Guaiac FOBTs detect the haem moiety of haemoglobin molecules by making use of the pseudoperoxidase activity of haem; haem releases oxygen from hydrogen peroxide (the developer), which then reacts with the colourless guaiac to form a blue dye.[30, 33, 36] The testing process generally requires that the patient applies two distinct samples taken from each of three separate bowel movements onto three test cards (or slides) each of which contains two windows lined with guaiac paper. The cards are developed in a physician's office or clinical laboratory. If any of the six windows are positive they turn blue. In the UK Pilot a triple test, integrated single card method was used, where test cards with one to four blue windows (called spots in the UK Pilot) were called 'weak

positive' and participants with 'weak positive' results were asked to complete a second test. If this repeat test had any positive spots, then the final result was considered to be positive.[26] If this second test had no positive spots, a third test was done to confirm a negative result. When five or six positive windows were present in the first kit, the result was considered positive without repeat testing. Regardless of the number of spots that are required before a patient is considered positive, all tests deemed to be positive should be followed by a colonoscopy.[12, 36]

Guaiac tests are generally best at detecting large, more distal lesions. Because they depend upon peroxidase or pseudo-peroxidase activity in the faeces, and are not specific to the pseudoperoxidase activity of human haemoglobin, many variables are said to influence their results. These include dietary factors, for example animal haemoglobin/myoglobin in red meat, fruits and vegetables high in peroxidase activity (false-positive results), high doses of vitamin C (false-negative results), aspirin or other medication that may cause gastrointestinal bleeding (false-positive results) and faecal hydration.[12, 30, 34] The drying out of the faecal specimen and exposure to high ambient temperature can also result in false negative findings.[23, 30, 34, 36] Conversely rehydration of the sample may deactivate the peroxidases from fruit and vegetables reducing the number of false positive results. A systematic review of five RCTs of CRC screening using a guaiac test (Haemoccult) suggested that mild-to-moderate dietary restriction during unrehydrated FOBT may not be necessary as it did not appear to affect positivity rates and completion rates.[37] However, the review did not include evidence on the use of more recent guaiac tests such as Haemoccult Sensa, which are believed to be more susceptible to the effects of diet. It also failed to account for dietary differences between countries and ethnic groups.[23, 30, 36]

Studies included in this review used the following guaiac tests:

Haemoccult
In this test, pseudoperoxidase activity converts colourless guaiac to blue in the presence of a developer that contains hydrogen peroxidase. The test produces a qualitative yes or no result, with a positive result being defined as a blue colour diffused into a 0.5 cm margin around the stool specimen within one minute of developer application.[38] Development is performed in the laboratory or in the medical office. Studies have shown that accurate test interpretation requires training, particularly for borderline results.[39] Two versions of this test are considered together in this review: Haemoccult and Haemoccult II, and are referred to as Haemoccult throughout.

The literature describes the two major limitations of Haemoccult as low sensitivity and the need for dietary restrictions. Although re-hydration has been used to increase sensitivity in the past, it has been abandoned because it seems to alter the concentration of the developer used and thus produces an unacceptible increase in false-positive results.[38] The current review used regression analysis to evaluate the impact of re-hydration and dietary restrictions on the overall diagnostic accuracy (as indicated by the DOR) of Haemoccult.

Haemoccult Sensa
Haemoccult Sensa differs from Haemoccult in that it uses an enhancer to allow detection of lower levels of peroxidase activity.[38] The manufacturer's definition of a positive result is the same as that for Haemocult. According to the manufacturer, Haemoccult Sensa produces a more stable and readable positive result than Haemoccult.[38] Haemoccult Sensa is apparently very sensitive to peroxidases and dietary restrictions have been recommended with its use.[23] The manufacturer states that Haemoccult Sensa slides can be either prepared and developed immediately or prepared and stored for up to 14 days at controlled room temperature (15 to 30^{o}C) before being developed.[38] Waiting several days may allow unstable vegetable peroxidase to break down, leaving only the pseudo-peroxidase activity attributable to haemoglobin.[38] This strategy may reduce the number of false-positive results.

Shionogi B
The only available information was that the test is produced by *Shionogi Pharmaceutics Co*., in Osaka, Japan.

KryptoHaem
The test has been produced in Germany, but no further information is currently available.

1.3.2 Immunochemical FOBTs

Immunochemical FOBTs are said to be more sensitive because they use monoclonal or polyclonal antibodies raised against the globin moiety of human haemoglobin, detecting intact human haemoglobin or its very early degradation products.[31] They avoid interference from compounds which are known to affect the guaiac tests. Labelled antibody attaches to the intact globin antigen, resulting in a positive test result.[40] The globin protein does not remain intact after passage through the upper gastrointestinal tract. Therefore, a positive immunochemical FOBT is specific for bleeding in the lower gastrointestinal tract.[23, 30, 36, 40] Current studies report positive test results of between 3% and 6% of screened populations.[23, 30, 33, 36, 41] Greater sensitivity also has the potential to increase the number of false-positive tests (decreased specificity) due to the detection of physiological blood loss.[31]

Immunochemical FOBTs are more expensive than guaiac tests. However, it has been suggested that the greater cost may have a minimal effect on cost-effectiveness of screening in the long-term, if they detect more CRC in early stages.[12, 38, 40]

Studies included in this review used the following immunochemical tests:

Feca-EIA

Feca-EIA is a test kit based on the enzyme immunoassay (EIA) method used for the detection of occult blood in the faeces. It seems that it was produced by Nordic Pharmaceuticals, but is no longer available for use and no relevant information was found in the studies using this test.[1, 2] Two other tests using the enzyme immunoassay (EIA) method are evaluated together in the current review: Hemo-EIA and Stick-EIA.

FlexSure

This test has the advantage of simplicity and can be developed by a clinician or a laboratory technician. FlexSure (Beckman Coulter, Inc., Palo Alto, CA) is based on the specific binding of human haemoglobin to human haemoglobin antibody.[38] In the test device, antihuman haemoglobin is immobilised in a test strip. In the presence of antihuman haemoglobin conjugate, human haemoglobin migrates chromatographically along the test strip to the test line.[38] If the test is positive a visible line appears, indicating the presence of human blood in the stool sample. The absence of this line indicates a negative test. The test procedure takes about five minutes and must be interpreted immediately to be accurate.

Because FlexSure results need to be interpreted immediately, this test might not be easily applicable for screening large populations.[38] In addition, FlexSure is no longer commercially available in the USA or UK.

Immudia HemSP

The Immudia HemSp test (Beckman Coulter, Inc., Palo Alto, CA) is based on a reverse passive haemagglutination.[42, 43] This assay uses fixed chicken erythrocytes coated with antihuman haemoglobin-immunized rabbit serum. These erythrocytes agglutinate in the presence of human haemoglobin in faecal specimens.

Immudia HemSp consists of a test card similar to Haemoccult, but with a wider area for sample placement. The specimen placement area consists of many small disks. The test subjects are instructed first to make a thin faecal smear on the test filter paper. A diluent is added for development and the specimen is incubated at room temperature for 30 minutes before results are interpreted. Samples showing agglutination at a dilution of 1:8 are interpreted as a positive result.

Other versions of the same test are: HemeSelect, RPHA, and Magstream HemSp. The latter is an automated version using magnetic gelatine particles. Immudia HemSp is manufactured in Japan by Fujirebio and in Western countries by Beckman Coulter. Although this test has been approved for use in the USA by the FDA, its use was discontinued. The automated version of the Immudia HemSp test, Magstream HemSp, is currently being used in Australia. It is not clear if it is currently available in the UK.

Iatro Hemcheck

This is a latex agglutination inhibition assay.[42] The tip of a collection stick is pushed into the stool at several different points, and sealed in a small plastic tube containing buffer.[42] One drop of the faecal

liquid is put in a well and mixed with anti-human-haemoglobin antibody attached to latex particles. Samples are classified as positive when no agglutination occurs within 1.5 minutes of completion of the test procedure, and negative when agglutination occurs.[42]

LA Hemochaser
This is a latex agglutination assay. The test aims to detect transferin as well as human-haemoglobin. Stool is collected in the same way as the stool collection for the Iatro Hemcheck test. One drop of the faecal liquid is put in a well and mixed with anti-human-haemoglobin antibody attached to latex particles. Samples are classified as positive when agglutination occurs after three minutes, and negative when no agglutination occurs.[42]

MonoHaem
According to the manufactures, MonoHaem incorporates an immobilised monoclonal antibody on a slide which selectively binds human haemoglobin from the faecal sample (http://www.chemicon.com/Product/ProductDataSheet.asp?ProductItem= 991040995). After application of the sample to the slide, the bound haemoglobin is detected using an aqueous ethanolic solution of gum guaiac followed by hydrogen peroxidase. The gum guaiac resin contains alpha guaiaconic acid which is oxidised in the presence of peroxide to a blue coloured product by the pseudoperoxidase enzymatic action of haemoglobin. Because the haemoglobin is bound selectively by the localised monoclonal antibody on the slide, a positive reaction appears as a blue ring or spot confined to the area of antibody immobilisation. The manufactures describe a positivity rate of 2.4% and a false positive rate of 1 to 3% for MonoHaem.

OC Light
This is a latex agglutination assay.[42] Stool sampling methods are the same as those of Iatro Hemcheck.[42] Two drops of the faecal liquid are put in the well and mixed with anti-human-haemoglobin antibody attached to polystyrene latex particles. Samples are classified as positive when agglutination occurs three minutes after completion of the test procedure, and negative when no agglutination occurs.[42] The haemoglobin concentration can be calculated at a rate of 90 measurements per hour with the OC-Sensor system, and various positivity thresholds can be set.[44]

Other versions of the same test are: OC Hemocatch, OC Hemodia and LAT. This test did not receive an approval by the FDA in the USA. OC Light is manufactured by Eiken Chemical in Japan.[45] The test is not apparently available in the UK.

Ouchterlony
No information about the characteristics of this test is available.

SPA test
This assay uses human haemoglobin antibody coated staphylococcal protein A co-agglutination.[46] Stool sampling methods are the same as those of Iatro Hemcheck. After collection, one drop of the faecal liquid and a drop of SPA reagent are put on a glass plate (1% staphylococcus coated with human haemoglobin antibody) and mixed. Samples are classified as positive when agglutination occurs after one to three minutes from completion of the test procedure, and negative when no agglutination occurs.[46]

2. RESEARCH QUESTIONS

The aim of this project was to carry out a systematic review to determine the most accurate and/or cost-effective FOBT, or combination of FOBTs, for use in an average risk population invited to undergo screening for colorectal neoplasms (adenomas and cancers). This review takes as its starting point the assumption that screening for colorectal neoplasms, in an average risk population, using FOBT, is an effective and cost-effective strategy, (see Section 1.2).

The specific objectives of the review were:

- To determine the diagnostic accuracy of different types of FOBTs (singly or in combination) when used in an average risk population to screen for colorectal neoplasms.
- To determine the cost-effectiveness of different types of FOBTs when used in an average risk population to screen for colorectal neoplasms.
- To determine whether further studies are necessary in order to evaluate the relative diagnostic accuracy of FOBTs.

3. REVIEW METHODS

An advisory panel was established. In addition to providing subject-specific input during the review, members of the panel were invited to offer comment on the protocol and draft report. Details of advisory panel members can be found in Appendix A. The systematic review was performed in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[11] and published guidelines on the meta-analysis of diagnostic tests.[47-53]

A list of FOBT tests, along with any known manufacturers and UK distributors is given in Appendix B. Studies included in the review evaluated the following FOBTs:

1. Guaiac tests: Haemoccult, Haemoccult Sensa, KryptoHaem, and Shionogi B.
2. Immunochemical tests: Feca-EIA, Hemo-EIA, Stick-EIA, FlexSure , Immudia HemSp, Iatro Hemcheck, LA Hemochaser, MonoHaem, OC Light, Ouchterlony, and SPA test.

3.1 Search strategy

A database of published and unpublished literature was assembled from systematic searches of electronic sources, handsearching, and consultation with experts in the field. The database was built using the EndNote 6 software package.

A Medline search strategy was devised and after exploring a series of sensitive search strategies, a more precise strategy was chosen that attempted to maximise capture of relevant records whilst excluding large numbers of irrelevant records. The MEDLINE search strategy was than translated and adapted as appropriate for each database searched. Details of the search strategies are presented in Appendix C. All databases were searched from inception to the most recent date available. There were no restrictions by country, language, publication date or study design.

The following databases were searched: MEDLINE, EMBASE, BIOSIS, Pascal, Science Citation Index (SCI), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HEED), NHS Economic Evaluation Database (NHS EED), and Latin American and Caribbean Literature on the Health Sciences (LILACS). In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of relevant databases including Inside Conferences, Systems for Information in Grey Literature (SIGLE), Dissertation Abstracts, the National Research Register (NRR), National Technical Information Service (NTIS) and the GrayLit Network.

Internet searches were also carried out using a specialist search engine (OMNI: http://www.omni.ac.uk/), a general search engine (Google: http://www.google.co.uk/), and a meta-search engine (Copernic: http://www.copernic.com/).

Hand searches of the following key journals were performed: Gastroenterology (January 1965 to December 2004), Scandinavian Journal of Gastroenterology (January 1998 to December 2004), American Journal of Gastroenterology (January 1998 to December 2004), Cancer (January 1996 to January 2005) and Journal of Medical Screening (January 1997 to December 2004). In addition, hand searches of the following conference proceedings were carried out: *Prevention screening and management of the colonic cancers* (conference of consensus), Paris, France, 29th January 1998; *Cancer research at the European level*, Brussels, Belgium, September 1994; *Colon examination study in Japan*, 12th Meeting, Chiba, Japan, Oct 1994; *Annual Meeting of the British Society of Gastroenterology*, Birmingham, UK, March, 2003.

The reference lists of included studies and any systematic reviews identified were also searched to identify further potentially relevant studies.

3.2 Inclusion and exclusion criteria

Two reviewers (KSW, JB) independently screened titles and abstracts for relevance. Disagreements were resolved by consensus. Full papers of potentially relevant studies were obtained and assessed

for inclusion by one reviewer (JB). A predefined form with a checklist of explicit study selection criteria, constructed using Microsoft Access, was used to assess full papers for inclusion. All studies considered to be eligible for inclusion, and a random selection of studies considered not eligible were checked by a second reviewer (KSW). Any disagreements were resolved by consensus. Where consensus could not be reached, a third reviewer was consulted (JK). Appendix D provides details of the procedure used for selecting studies.

A predefined form with a checklist of explicit study selection criteria was constructed using Microsoft Access. This was based on the categories described in Appendix E. The checklist was piloted in 20 studies and adapted as necessary. There were separate inclusion and exclusion criteria for studies of diagnostic accuracy and economic evaluations.

3.2.1 Inclusion criteria for FOBT diagnostic accuracy studies

Study design: Any study evaluating diagnostic accuracy of FOBTs where FOBT results were compared with those of a reference standard (diagnostic cohort and diagnostic case-control studies). Randomised and non-randomised controlled trials comparing the efficacy of screening of two or more FOBTs were also eligble for inclusion; for these studies the results for the intervention arm (screened population) were treated as a diagnostic cohort. Diagnostic cohorts derived from trials were only included where the drop out rate, from the intervention arm, was less than 15%.

Population: Average risk adult population. Studies conducted in high-risk populations (e.g., family history of CRC, polyposis, symptomatic) were excluded.

Index tests: Any guaiac or immunochemical FOBT used (singly or in combination) in the identification of CRC or adenomatous polyps, whether or not dietary restrictions were imposed. Studies evaluating flushable FOBTs and/or further stool markers currently being developed, such as detection of mutated DNA, tests for albumin, and calprotectin were excluded.

Reference standard: Diagnostic cohort studies, including cohorts derived from trials, were required to report details of the reference standard used; any reference standard was accepted. Screening trials had to report at least two screening rounds or, if a cancer registry/questionnaire was used as the reference standard, between three and ten years follow-up. Diagnostic case-control studies were included in the review whether or not the details of the reference standard used to verify disease status was reported.

Outcome measures: Studies were required to report sufficient information to construct a 2 x 2 table. Where sufficient data were available, separate 2 x 2 tables were constructed for the accuracy of the FOBT to detect all neoplasms, CRC, all adenomas, adenomas ≥1cm in size and adenomas ≤ 1cm in size. If a study evaluated more than one test, but only reported sufficient data to construct a 2 x 2 table for one FOBT, only data for that FOBT were included in the review. The secondary outcome of interest was adverse events related to the FOBT.

3.2.2 Inclusion criteria for economic evaluations of FOBTs

Study design: Full economic evaluations available on the NHS EED database were eligible for inclusion.

Population: Average risk adult population. Studies conducted in a high-risk population (e.g., family history of CRC, polyposis, symptomatic) were excluded.

Intervention: Studies comparing at least two FOBTs were eligible for inclusion. Studies evaluating flushable FOBTs and/or further stool markers currently being developed, such as detection of mutated DNA, tests for albumin, and calprotectin, or evaluations that assessed a single FOBT were excluded. Economic evaluations assessing the cost-effectiveness of CRC screening, where the programme happened to include FOBT testing, and economic evaluations that assessed a single FOBT were excluded.

Outcome measures: Economic evaluations where costs from a health service or broader (e.g. societal) perspective or appropriate health-related outcomes were reported were eligible for inclusion.

3.3 Data extraction

Data extraction forms were developed using Microsoft Access. These were piloted on a small selection of studies. Data extraction was performed by one reviewer (KSW) and checked by a second (JB). Any disagreements were resolved by consensus. Where consensus could not be reached, a third reviewer was consulted (JK). Papers in French, Portuguese, Italian, Spanish were extracted by one reviewer (KSW) and the data were entered directly into the Access database. Other non-English language papers (Chinese, Japanese, Dutch, German, Czech, Polish, Hungarian) were extracted by one reviewer (JB), accompanied by a speaker of that language, and the data were entered directly into the Access database. A second reviewer did not check non-English language studies.

3.3.1 Diagnostic accuracy studies

The following information was extracted for studies used to assess the diagnostic accuracy of FOBTs:

Study details: Study identifier (EndNote ID), author, year, country, setting, study design, aim of the study, number of participants, and duration of follow up.

Population details: Description of the participants included in the study (age, gender, ethnicity, and other potential risk factors), predefined inclusion and/or exclusion criteria, dietary restriction, method of patient selection, disease prevalence, and number of participants recruited/included in the study.

Details of index test: Test evaluated (guaiac or immunochemical (IC), IC test/methodology (e.g., passive haemagglutination, latex agglutination), details of test execution, name of test (preferably as it is used in the UK), method and location of development, method and number of stools collected, frequency of tests, time between specimen collection and development and storage conditions if there was any delay, faecal haemoglobin limit of detection (for IC tests), and definition of positive test.

Details of reference standard: Reference standard used for both positive and negative FOBT result (e.g., colonoscopy, flexible sigmoidoscopy, follow up), and number of patients that completed the reference standard.

*Outcome details***:** Data were used to construct a 2 x 2 table (true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN). Data on adverse events was also extracted.

3.3.2 Economic evaluations

For economic evaluations, data were extracted on the tests being compared, study population, the time period over which the study was performed, measures of effectiveness, direct costs (medical and non-medical), production costs, resource use, currency, results and details of any decision modelling and sensitivity analysis.

3.4 Quality assessment

Quality assessment forms were developed using Microsoft Access. Quality assessment was carried out independently by two reviewers (KSW, JB). Any disagreements were resolved by consensus. The quality of French, Italian, Portuguese and Spanish papers was assessed by one reviewer (KSW), and Chinese, Czech, Dutch, German, Hungarian, Japanese and Polish by one reviewer (JB) accompanied by a speaker of the language.

The results of the quality assessment were used for descriptive purposes to provide an indication of the common quality issues across the included studies and to provide a transparent method of recommendation for design of future studies. In addition, where sufficient data were available, quality components were included as explanatory variables in regression analyses to investigate possible associations with diagnostic accuracy.

3.4.1 Diagnostic accuracy studies

Diagnostic cohort studies, including cohorts derived from trials, and diagnostic case-control studies were assessed for methodological quality using the assessment tool for diagnostic studies (QUADAS).[47] The sources of bias assessed using this tool include spectrum bias, selection bias, appropriateness of reference standard, verification bias, review bias, and clinical review bias. Two criteria, the avoidance of disease progression and incorporation bias, were not scored as they were

deemed irrelevant to this topic. The QUADAS tool together with details on how studies were scored is provided in Appendix F.

3.4.2 Economic evaluations

The quality of the economic evaluations was assessed according to a checklist developed by Drummond et. al. (2000).[54] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Clinical Excellence.[54]

3.5 Synthesis

FOBT characteristics were identified from manufacturers information and from the FDA registered haematology medical devices list[55] Results were analysed according to the specific FOBTs being evaluated. Within these groups, tests were analysed according to the target condition (all neoplasms, colorectal cancers, all adenomas, and adenomas $\geq$ 1cm). For each data set the sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DOR) were calculated, with 95% CIs, using MetaDisc.[56]

DOR were calculated as the Odds (Sensitivity) / Odds (1-specificity), or ad/bc in a 2 x 2 table. DOR have the advantage of being a single indicator of diagnostic accuracy in contrast to most of the other measures, which have to be judged in pairs. The DOR can take values between 0 and infinity, with high values indicating good test performance.[53, 57] To account for 0 cells in the 2 x 2 tables, 0.5 was added to every cell for all 2 x 2 tables as recommended by Moses et. al. (1993).[57]

Whenever more than four studies were included for a specific FOBT and target condition, individual study results were presented graphically in ROC space. Between study heterogeneity of the sensitivity, specificity, likelihood ratios and DOR was investigated using the Cochrane Q statistic[58] and through visual examination of Galbraith plots of study results.[59] We measured the impact of heterogeneity (I^2) in the meta-analyses.[60] I^2 describes the proportion of total variation in study estimates that is due to heterogeneity and can be calculated from the Cochran Q statistics.[60, 61] The following equation was used to calculate I^2:

$$I^2 = 100\% \times \frac{Q - \mathrm{df}}{Q}$$

and data were not pooled where I^2 was above 75%.[61] Since I^2 was above 75% in all data sets, no pooled estimates are presented. Where more than ten data sets were available for any one grouping of test type and target condition, heterogeneity was further investigated using the Moses-Shapiro-Littenberg method for meta-regression analysis.[56, 62] For these data sets sROC curves were estimated, using the following equation:

$$Sen = \frac{1}{1 + \frac{1}{e^{\frac{a}{1-b}} \times \left(\frac{1 - Spe}{Spe}\right)^{\frac{1+b}{1-b}}}}$$

a and b were calculated using the following regression equation:

D = a + bS
D = [logit (TPR) – logit (FPR)] = log (DOR)
S = [logit (TPR) + logit (FPR)}]

Logit (TPR) = ln(TPR/(1-TPR))
Logit (FPR) = ln(FPR/(1-FPR))

This was estimated by regressing D against S, weighting according to sample size, for each study. Beta provides an estimate of the extent to which D is dependent on the threshold used. If beta is 0 (when line is symmetric with respect to the line TPR = 1 – FPR), or not significantly different from 0, then the DOR is not affected by the threshold used. When this was the case the DOR was pooled according to standard methods for pooling odds ratios.[53, 62] In such cases the following equation was used to calculate the SROC curves:

$$Sen = \frac{1}{1 + \frac{1}{DOR_T \times \left(\frac{1 - Spe}{Spe} \right)}}$$

The sROC model outlined above was extended to include the following covariates.[63]

- Factors affecting the index test (for example: rehydration of the stool specimen, dietary restrictions prior to testing)
- QUADAS items[47]

Initially univariate analysis was performed with items included individually in the model. Items which showed a significant association with D at the 10% significance level were investigated further using step-wise multivariate models; a minimum of ten data sets per variable entered were pre-requesit for multivariate modelling. In this approach, all items found to be significant in the univariate models were entered into the multivariate model, weighted by sample size, and then dropped in a step-wise fashion with the least significant item dropped first. The final model was achieved when all items remaining in the model showed a significant association with D at the 5% level. All analyses were performed using random effect models in the MetaDisc software (version 1.3).[56]

3.5.1 Economic evaluations

Narrative summaries were produced for each full economic evaluation, comparing two or more FOBTs, identified.

4. RESULTS OF THE REVIEW

4.1 Results of the literature searches

The literature searches identified 3,259 references. Of these, 1089 were considered to be potentially relevant and ordered. Figure 1 shows the flow of studies through the review process and the number of studies excluded according to each of the inclusion criteria. Appendix G gives details of the studies included in the review, and appendix H lists the studies that were excluded from the review, with the reason for exclusion. Appendix I details on which database(s) each included study was identified.

We identified 130 studies that evaluated the diagnostic accuracy of either a guaiac or immunochemical FOBT in a screening population, and 86 trials that assessed the efficacy of screening with FOBT compared to no screening. Of these, 17 were designed as diagnostic cohort studies[64-80] and 21 diagnostic case control studies[1-4, 6, 7, 9, 10, 42, 81-92] and were included in the review. In addition, 17 screening trials,[5, 8, 46, 93-106] seven RCTs[107-113] and seven economic evaluations [114-120] also met the inclusion criteria. Therefore, a total of 69 studies were included: 59 provided data on the diagnostic accuracy of FOBTs, three described adverse events related to the use of FOBTs, and seven reported economic evaluations comparing at least two FOBTs.

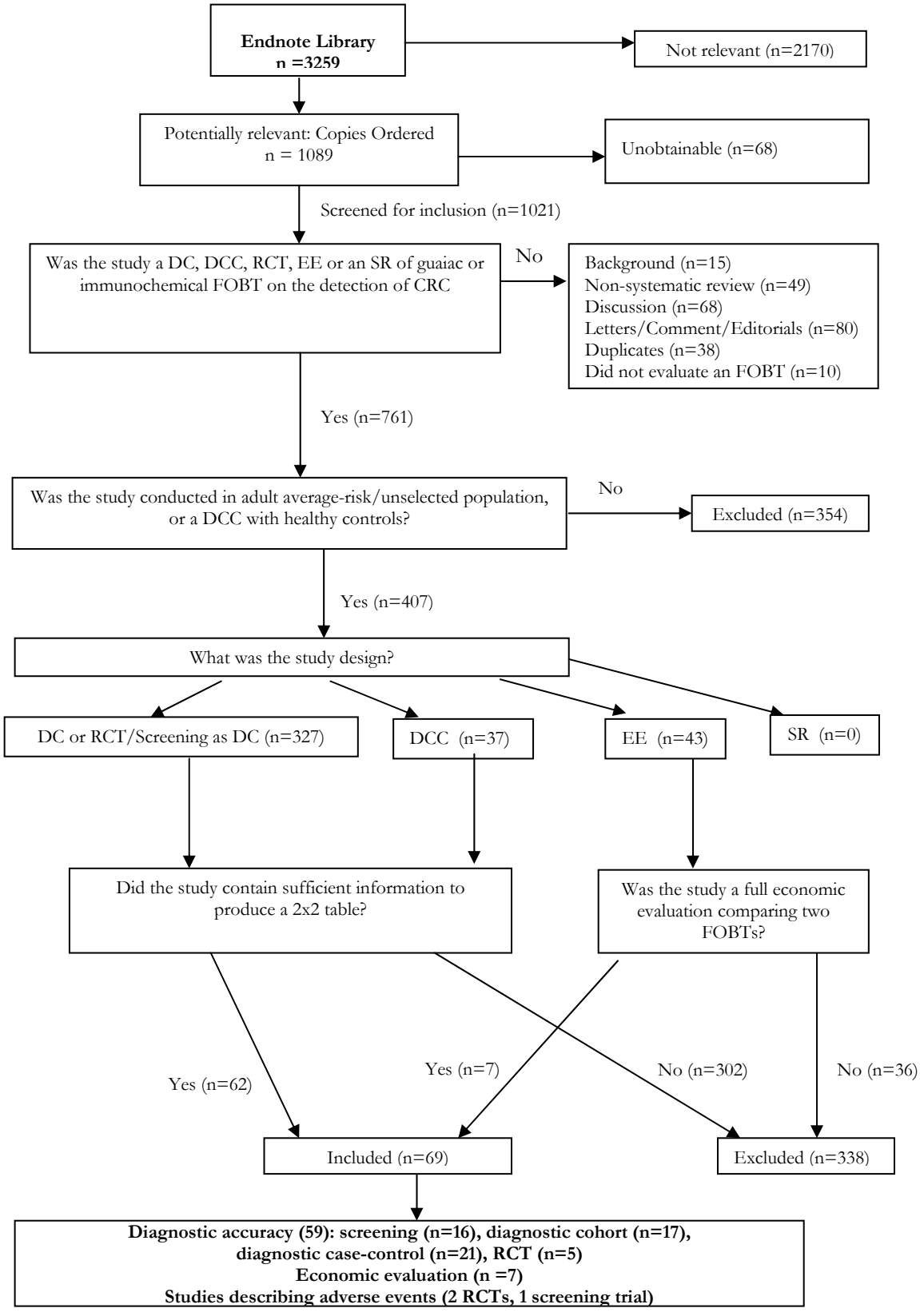
Thirty-four of the studies evaluating diagnostic accuracy were conducted in Asia (China, Hong Kong, Japan, Korea, Singapore and Taiwan), two in Australia, 13 in Europe (UK, Denmark, France, Republic of Ireland, Italy, Norway and Sweden), 11 in the USA, and two were conducted in Israel. The two studies conducted in the UK provided details of adverse events only.[104, 111] Of the economic evaluations, two were conducted in Asia, two in the UK, two in other European countries, and one in the USA. Six studies were available only as abstracts.[78, 81, 93, 99, 101, 103] A total of 317 non-English language papers were assessed for this review: seven Chinese, one Croatian, six Czech, five Danish, three Dutch, 85 French, 97 German, one Hebrew, one Hungarian, 29 Italian, 65 Japanese, one Portuguese, and 16 Spanish. Two Chinese,[84, 91] two German[68, 83] and eight Japanese[1-4, 6, 82, 89] papers met the inclusion criteria and were translated. We were unable to locate full papers for 68 references. The majority of these were identified through handsearching and were published in either German or Japanese during the 1980s. Attempts were made to contact the authors of these papers without success.

Twenty three of the included diagnostic accuracy studies evaluated guaiac FOBTs,[64, 65, 67-70, 72, 77-81, 83, 93, 94, 97, 100, 105-107, 110, 112, 113] 25 immunochemical FOBTs,[42, 46, 66, 71, 73-76, 82, 85-92, 95, 96, 98, 99, 101-103, 108] 10 evaluated both types of FOBT[1-10] and one evaluated a guaiac and immunochemical FOBT in sequence and did not report results for the two FOBTs separately.[84] Three studies provided data for adverse events only.[104, 109, 111] Six of the economic evaluations evaluated both guaiac and immunochemical FOBTs[115-120] and one evaluated two guaiac FOBTs.[114]

The included studies evaluated the following FOBTs:
Guaiac FOBTs: Haemoccult, Haemoccult II, Haemoccult Sensa, KryptoHaem, and Shionogi B.
Immunochemical FOBTs: Checkmate Hemo, Feca-EIA, Hemo-EIA, Stick-EIA, FlexSure, HemeSelect, Immudia HemSp, Imdia HemSp, Magstream HemSp, RPHA, Iatro Hemcheck, LA Hemochaser, MonoHaem, OC Hemodia, OC Hemocatch, OC Light, LAT, HB Latex, Ouchterlony and the SPA test.

4.2 Guaiac FOBTs

Five guaiac-baed FOBTs were evaluated in the included studies, Haemoccult, Haemoccult II, Haemoccult Sensa, KryptoHaem and Shionogi B. The results of Haemoccult and Haemoccult II were grouped together, and are referred to as Haemoccult throughout the review. The number of participants ranged from 44 to 97,205. The gender differential was not reported in 19 studies, but where reported, the proportion of males ranged from 40.7% to 100%. Twenty seven studies did not report a mean age of the participants. Of those that did, the mean age ranged from 40 to 68 years. Where a mean age was not reported, only sixteen studies reported the age range of the participants. The youngest participants included were 13 years in the control group of a diagnostic case control trial, and 20 years in a diagnostic cohort study. The oldest participants were were 89 years in the case group of a diagnostic case control trial, and 88 years in a diagnostic cohort study.



DC: Diagnostic cohort; DCC: Diagnostic case-control; RCT: Ranopmised controlled trial; EE: Economic evaluation; SR: Systematic review.

Figure 1: Flow chart of studies through review process

Of the 31 studies that evaluated a named guaiac FOBTs, 17 imposed dietary restrictions before testing,[8, 10, 64, 65, 67, 68, 72, 77-79, 94, 97, 100, 105, 106, 110, 113] four did not,[4, 7, 69, 80] one study imposed restrictions on repeat testing only,[107] and nine provided no information regardingdietary restrictions.[3, 5, 6, 9, 70, 81, 83, 93, 112] Of the 23 studies that evaluated Haemoccult, four re-hydrated the slides before analysis,[70, 97, 107, 110] fourteen did not re-hydrate the slides,[7, 8, 64, 65, 69, 77, 78, 80, 93, 94, 100, 106, 112, 113] one rehydrated the slides from some people and not for others,[67] and four provided no information on the rehydration status of the slides.[6, 9, 79, 81] The other named guaiac FOBTs were developed either with rehydration,[68] without rehydration,[8, 72, 105] or the hydration status was not reported.[3, 4, 10, 83]

4.2.1 Quality

Of the 33 studies that evaluated the diagnostic accuracy of guaiac FOBTs, 11 were diagnostic cohort studies,[64, 65, 67-70, 72, 77-80] 10 were diagnostic case-control studies,[1-4, 6, 7, 9, 10, 81, 83] and 12 were either screening studies or RCTs from which a diagnostic cohort was derived.[5, 8, 93, 94, 97, 100, 105-107, 110, 112, 113] Figure 2 shows the proportion of guaiac FOBT studies that answered "yes", "no" and "unclear" to each one of the QUADAS items. Sixty nine percent of studies fulfilled the criteria for avoidance of partial verification bias, and 39% for the avoidance of differential verification bias. Forty two percent of studies detailed how people were selected for inclusion in the study and/or included an appropriate spectrum of patients. Thirty three percent of studies reported sufficient details on how the reference standard was performed, and 22% on how the index test was performed, to permit replication. Sixty four percent of studies failed to report sufficient details on clinical review bias, 42% on diagnostic review bias, and 50% on test review bias to judge whether these were avoided. Study withdrawals and handling of uninterpretable results were reported in over 70% of studies.

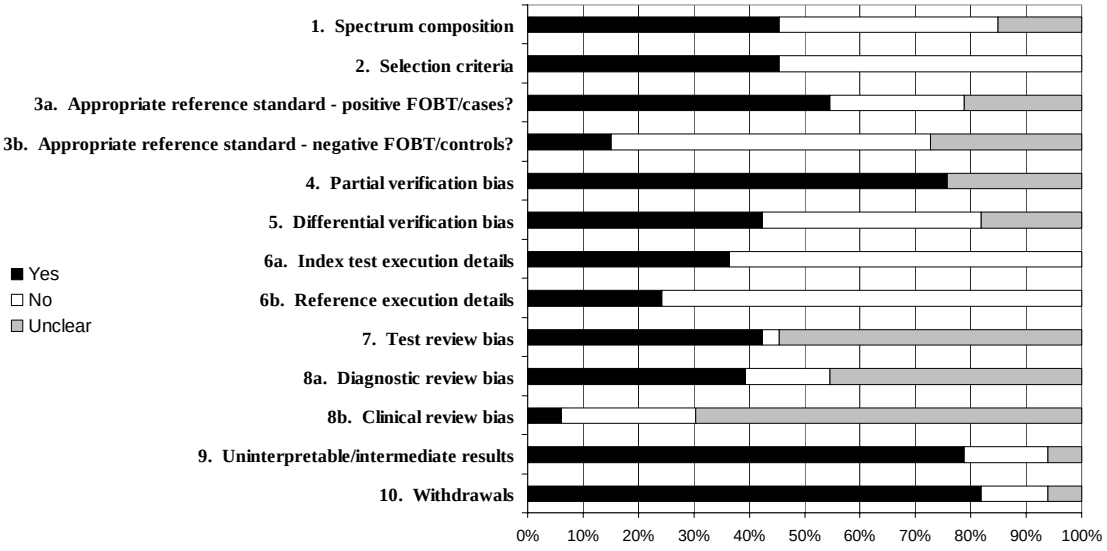


Figure 2: Proportion of guaiac FOBT studies rated as yes, no, or unclear on each of the QUADAS items

The reference standards used, where reported, varied considerably across the studies, with colonoscopy, barium enema, sigmoidoscopy or cancer registry used individually or in combination for people with a positive FOBT or cases. Colonoscopy, barium enema, sigmoidoscopy, cancer registry, follow-up or re-screening, individually or in combination, were used for people with a negative FOBT or controls.

4.2.2 Diagnosis of all neoplasms using guaiac FOBTs

Eleven diagnostic cohorts evaluated the diagnostic accuracy of guaiac FOBTs to detect all neoplasms. Nine evaluated Haemoccult,[64, 65, 67, 70, 77, 78, 80, 97, 113] one Haemoccult Sensa[5] and one Kryptohaem.[68] The reference standards used for people with a positive FOBT included colonoscopy,[5, 70, 77, 80, 97] colonoscopy and barium enema (in some or all participants),[113] colonoscopy and barium enema and rigid sigmoidoscopy,[78] colonoscopy or barium enema,[64, 65] with one study also referring to the cancer registry,[64] or sigmoidoscopy.[67, 68]

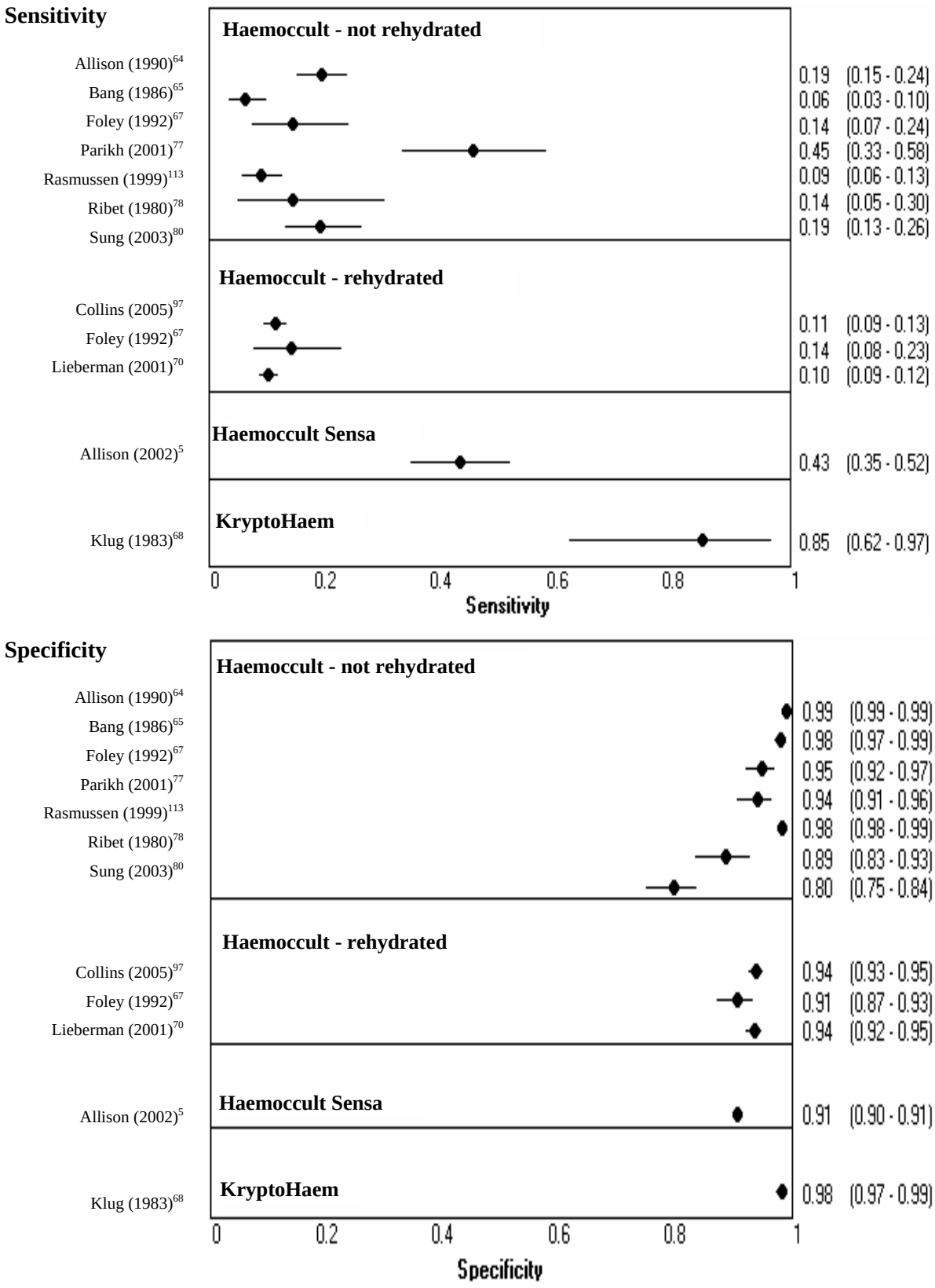


Figure 3: The sensitivity and specificity of guaiac FOBTs for the detection of all neoplasms as reported in diagnostic cohort studies

The reference standards used for people with a negative FOBT included colonoscopy,[80, 97] sigmoidoscopy,[65, 67, 68, 70, 77, 113] flexible colonoscopy,[5] sigmoidoscopy and barium enema,[78] or referral to the cancer registry.[64] Six cohort studies recruited an appropriate patient spectrum.[64, 67, 70, 77, 80, 97] Two studies did not name the guaiac FOBT used and therefore results are presented in table 1 but not included in the synthesis.[1, 2] There was statistically significant heterogeneity (Cochrane Q<0.05 and/or I^2>75%) between studies evaluating Haemoccult, therefore pooling was not undertaken.

Overall, Haemoccult had a low sensitivity, which ranged from 6.2% (specificity 98.0%) to 45.5% (specificity 94.0%) when three consecutive stool samples were examined. Comparing studies that rehydrated the Haemoccult slides with those that didn't, sensitivity ranged from 10.2% (specificity 93.6%) to 14.4% (specificity 90.5%) when rehydrated,[67, 70, 97] and 6.2% (specificity 98.0%) to 45.5% (specificity 94.0%) when not rehydrated.[64, 65, 67, 77, 78, 80, 113] Only one study reported results separately for both rehydrated and non-rehydrated Haemoccult FOBTs; the two tests were conducted on stool specimens from different people,[67] therefore no direct comparisons of rehydrated and non-rehydrated Haemoccult were available. Two cohort studies compared the accuracy of Haemoccult tests where samples were collected at home for three consecutive days to that of Haemoccult performed using a single stool specimen collected via a digital rectal examination (DRE).[77, 97] One study reported that both sensitivity and specificity were slightly better for the home test (Home: sensitivity 45.5%, specificity 94%; DRE: sensitivity 41.0%, specificity 92.8%).[77] The other study reported very low sensitivities for both tests, although this was slightly higher with the home test (Home: sensitivity 11.3%, specificity 93.9%; DRE: sensitivity 4.3%, specificity 97.5%).[97] Seven of the studies evaluating Haemoccult imposed dietary restrictions,[64, 65, 67, 77, 78, 97, 113] one did not[80] and one did not specify whether restrictions were imposed or not,[70] therefore it was not possible to evaluate the impact of dietary restrictions on the diagnostic accuracy of Haemoccult.

The study evaluating Haemoccult Sensa reported a higher sensitivity than all but one Haemoccult study (43.1%), although specificity was slightly lower than most of the Haemoccult studies (90.7%).[5] The study evaluating KryptoHaem reported the highest sensitivity (83.3%), and the second highest specificity (98.4%) of all the guaiac FOBTs evaluated for the detection of neoplasms in diagnostic cohort studies.[68] The main results are presented in figures 3 and 4, and all results are presented in table 1.

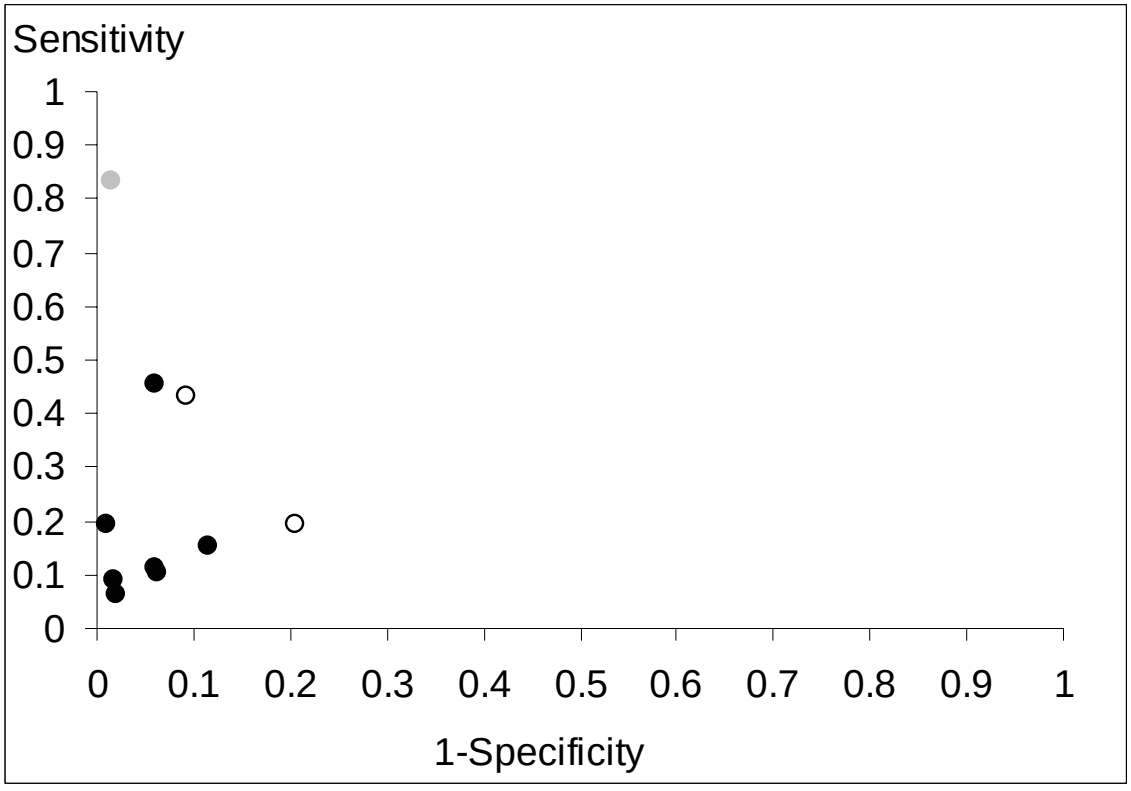


Figure 4: The detection of all neoplasms using Haemoccult (●), Haemoccult Sensa (○) and Kryptohaem (◍) based on the results of the diagnostic cohort studies.

Five diagnostic case-control studies evaluated the diagnostic accuracy of guaiac FOBTs for the detection of all neoplasms. Three evaluated Haemoccult,[9, 79, 81] one Haemoccult Sensa,[10] one Kryptohaem[83] and one Shionogi B.[9] Three studies used colonoscopy to verify disease status of both cases and controls,[9, 79, 81] one used colonoscopy to diagnose the condition in cases but the reference standard used to verify the disease-free status of controls was not reported,[10] and one did not report the reference standard used for either cases or controls.[83] No diagnostic case control study was deemed to have an appropriate patient spectrum. There was statistically significant heterogeneity (Cochrane $Q<0.05$ and/or $I^2>75\%$) between studies evaluating Haemoccult, therefore pooling was not undertaken.

In contrast to the results from the cohort studies, the diagnostic case control studies reported relatively high sensitivities for Haemoccult for the detection of all neoplasms, and lower specificities. Sensitivity ranged from 50.0% (specificity 50.0%) to 71.3% (specificity 66.2%), and specificity from 50.0% (sensitivity 50.0%) to 99.0% (sensitivity 65.2%).[9, 79, 81] None of the case-control studies reported whether the Haemoccult slides were rehydrated prior to developing or not. Haemoccult Sensa was reported as having a much higher sensitivity (72.2%) and specificity (99.0%) in the case control study than the cohort study.[10] The case-control study reported a similar specificity for the detection of neoplasms using Kryptohaem to that of the cohort study (98.4%), however, the sensitivity was much lower (47.4%).[83] Shionogi B was only evaluated in a case-control study, and was reported as having the highest sensitivity of the guaiac FOBTs evaluated using this study design, and the second highest when all studies were taken into consideration (73.4%).[9] However, this study reported the lowest specificity of all the guaiac FOBTs used to detect all neoplasms (60.3%). The main results are presented in figure 5 and 6, and all results are presented in table 1.

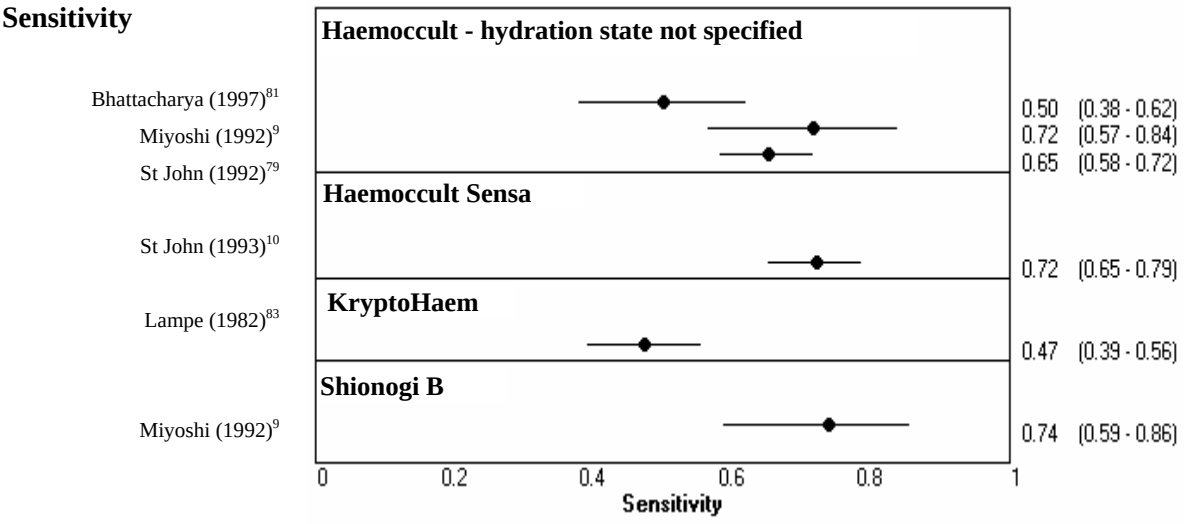


Figure 5a: The sensitivity of guaiac FOBTs for the detection of all neoplasms as reported in diagnostic case-control studies

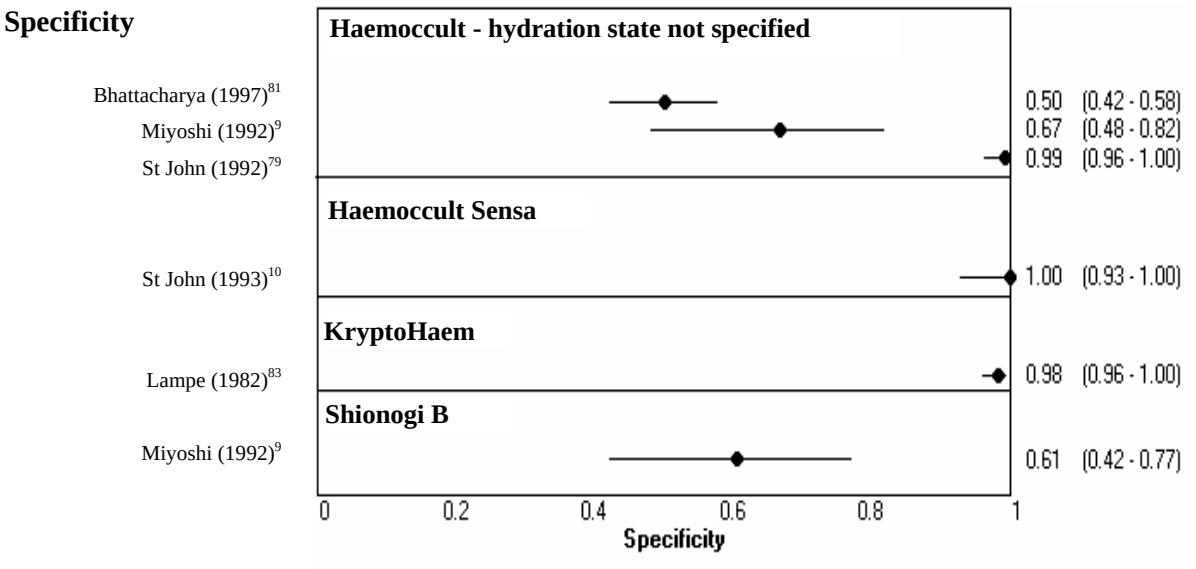


Figure 5b: The specificity of guaiac FOBTs for the detection of all neoplasms as reported in diagnostic case-control studies

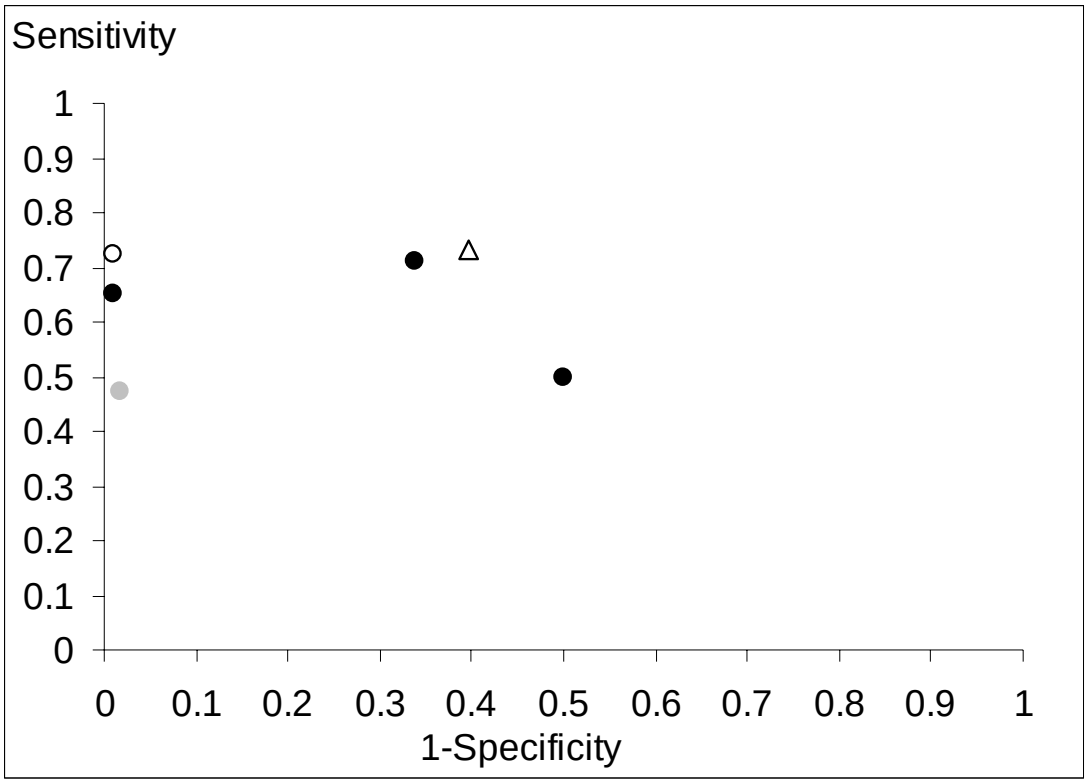


Figure 6: The detection of all neoplasms using Haemoccult (●), Haemoccult Sensa (○), Kryptohaem (◍) and Shionogi B (△) based on the results of the diagnostic case-control studies

4.2.3 Diagnosis of colorectal cancer using guaiac FOBTs

Nineteen diagnostic cohort studies evaluated the diagnostic accuracy of guaiac FOBTs for the detection of CRC. Sixteen evaluated Haemoccult,[8, 64, 65, 67, 69, 70, 80, 93, 94, 97, 100, 106, 107, 110, 112, 113] three Haemoccult Sensa[5, 8, 105] and one Shionogi B.[72] The reference standards used for people with a positive FOBT included colonoscopy,[5, 69, 70, 80, 97, 105, 112] colonoscopy and barium enema (in some or all participants),[110, 113] colonoscopy or barium enema,[64, 65] with one study also referring to the cancer registry,[64] colonoscopy and follow-up,[8] sigmoidoscopy,[67, 93, 94] sigmoidoscopy and barium enema[106] referral to the cancer registry,[72, 107] or GP contact, questionnaires and referral to the cancer registry.[100] The reference standards used for people with a negative FOBT included colonoscopy,[80, 97] sigmoidoscopy,[65, 67, 68, 70, 77, 93, 113] flexible colonoscopy,[5] sigmoidoscopy,[106, 107] referral to the cancer registry with follow-up,[8, 64] referral to the cancer registry,[69, 72, 100, 112] rescreening and referral to the cancer registry,[94, 105] or an annual questionnaire.[110] Ten studies recruited an appropriate patient spectrum.[8, 64, 67, 70, 80, 94, 97, 105, 107, 112] There was statistically significant between study heterogeneity (Cochrane Q<0.05 and/or I^2>75%) in all test groups, therefore pooling was not undertaken.

Overall, the accuracy of Haemoccult for detecting CRC appeared better than that for all neoplasms. The sensitivity of Haemoccult when three consecutive stool samples were examined ranged from 25.0% (specificity 98.74%) to 96.2% (specificity 99.2%) and the specificity ranged from 80.0% (sensitivity 30.0%) to 99.2% (sensitivity 96.2%).[7, 8, 64, 65, 67, 69, 70, 80, 93, 94, 97, 100, 106, 107, 110, 112, 113] Rehydrated Haemoccult slides produced sensitivities ranging from 27.1% (specificity 95.6%) to 89.1% (specificity 92.73%), and specificities from 89.9% (sensitivity 50.0%) to 95.6% (sensitivity 27.1%).[70, 97, 107, 110] Non-rehydrated Haemoccult slides had sensitivities from 25.0% (specificity 98.7%) to 96.2% (specificity 99.2%) and specificities from 80.0% (sensitivity 30.0%) to 99.2% (sensitivity 96.2%).[8, 64, 65, 67, 69, 80, 93, 94, 100, 106, 112, 113] Cohort studies that imposed dietary restrictions had sensitivities ranging from 7.4% (specificity 97.0%) to 100% (specificity 99.2%) and specificities from 90.0% (sensitivity 50.0%) to 99.2% (sensitivity 100%).[8, 64, 65, 67, 94, 97, 100, 106, 110, 113] The two cohort studies that did not imposed dietary restrictions reported sensitivities of 25.0% (specificity 80.0%)[80] and 58.0% (specificity 97.3%).[69] One study imposed restrictions on repeat testing only and reported a sensitivity of 26.1% and specificity of 95.6%.[107] Three studies did not specify whether restrictions were imposed or not.[70, 93, 112]

One study compared the accuracy of Haemoccult tests where samples were collected at home for three consecutive days to that of Haemoccult performed using a single stool specimen collected via a digital rectal examination (DRE), and reported that sensitivity was better with the home test (Home test: 34.1%, DRE: 8.0%), but specificity was slightly higher with the DRE test (Home test: 92.6%, DRE: 96.9%).[97] One study compared the accuracy of Haemoccult when one, two and three stools were tested, and reported an increase in sensitivity with the number of stools tested, from 83.3% (specificity 90.0%) when one stool was tested, to 95.2% (specificity 72.6%) when three were tested.[6]

Cohort studies of Haemocult for the detection of CRC was the only grouping with a sufficient number of data sets to support preliminary regression analyses. Neither sample rehydration nor dietary restrictions before the test were found to significantly affect overall accuracy (as indicated by DOR) in univariate analyses. When individual QUADAS items were considered, univariate analyses indicated that studies which adequately reported selection criteria and studies that adequately reported the details of how index tests were conducted had significantly lower accuracy than those that did not (RDOR = 0.30 (95% CI:0.10;0.89), p = 0.03 and RDOR = 0.24 (95% CI:0.06;1.00), p = 0.05, respectively).

The sensitivity of Haemoccult Sensa ranged from 62.2% (specificity 95.5%) to 78.6% (specificity 86.7%) and was therefore on the whole a more sensitive and less specific test than Haemoccult.[5, 8, 105] The one study that evaluated Shionogi B reported a sensitivity of 26.8% and specificity of 94.1%.[72] The main results are presented in figures 7 and 8, and all results are presented in table 1.

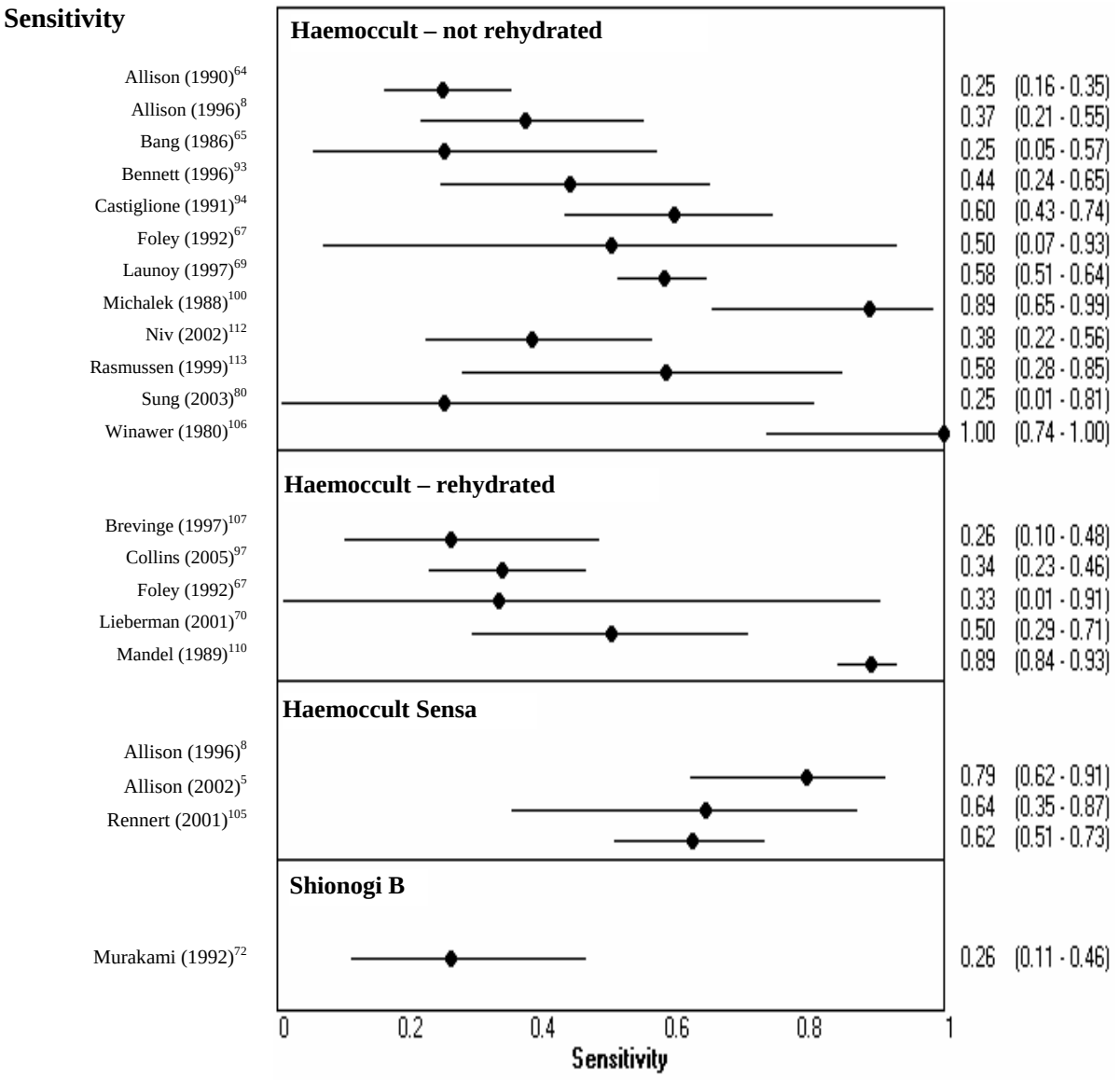


Figure 7a: The sensitivity of guaiac FOBTs for the detection of CRC as reported in diagnostic cohort studies

Specificity

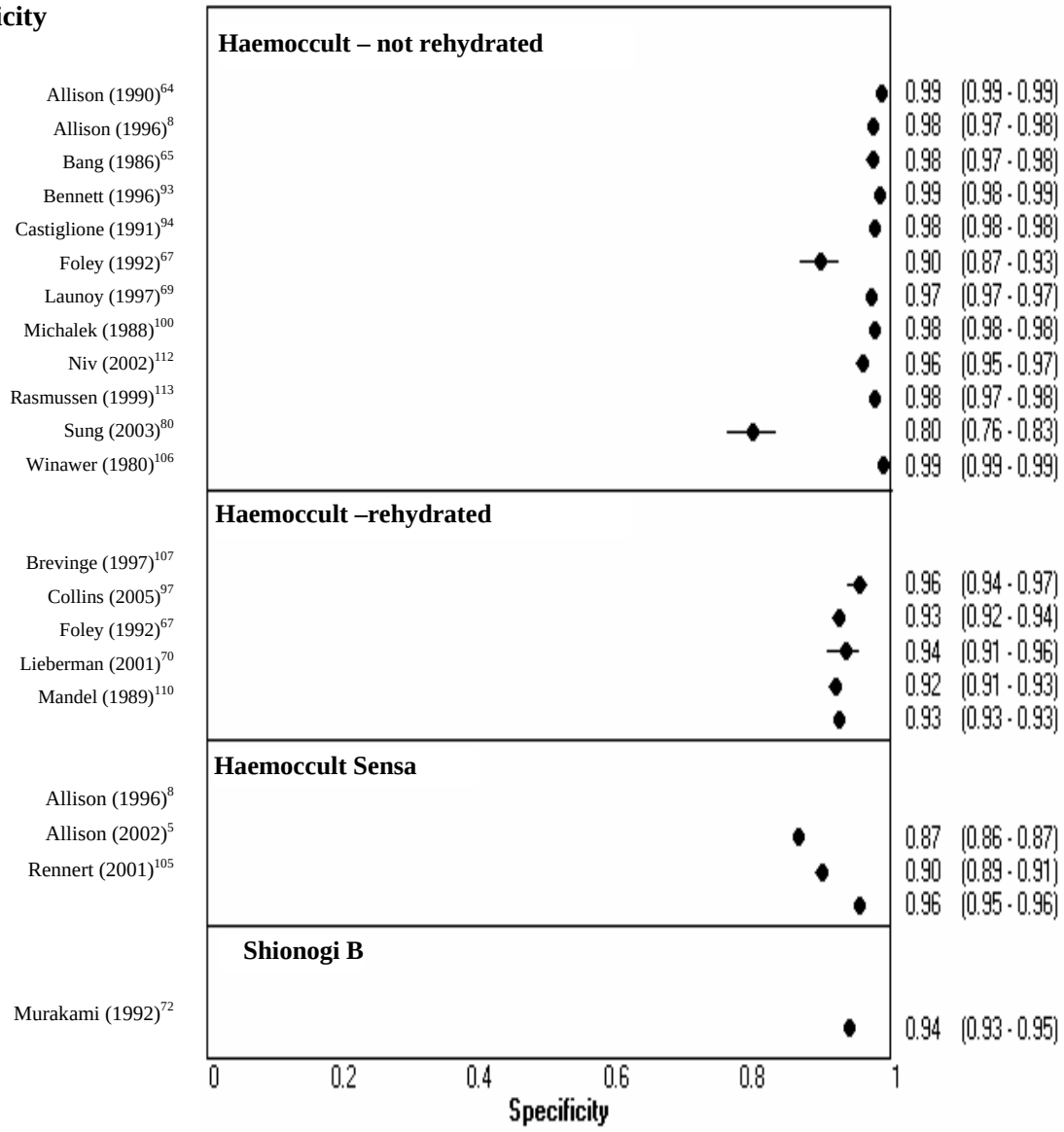


Figure 7b: The specificity of guaiac FOBTs for the detection of CRC as reported in diagnostic cohort studies

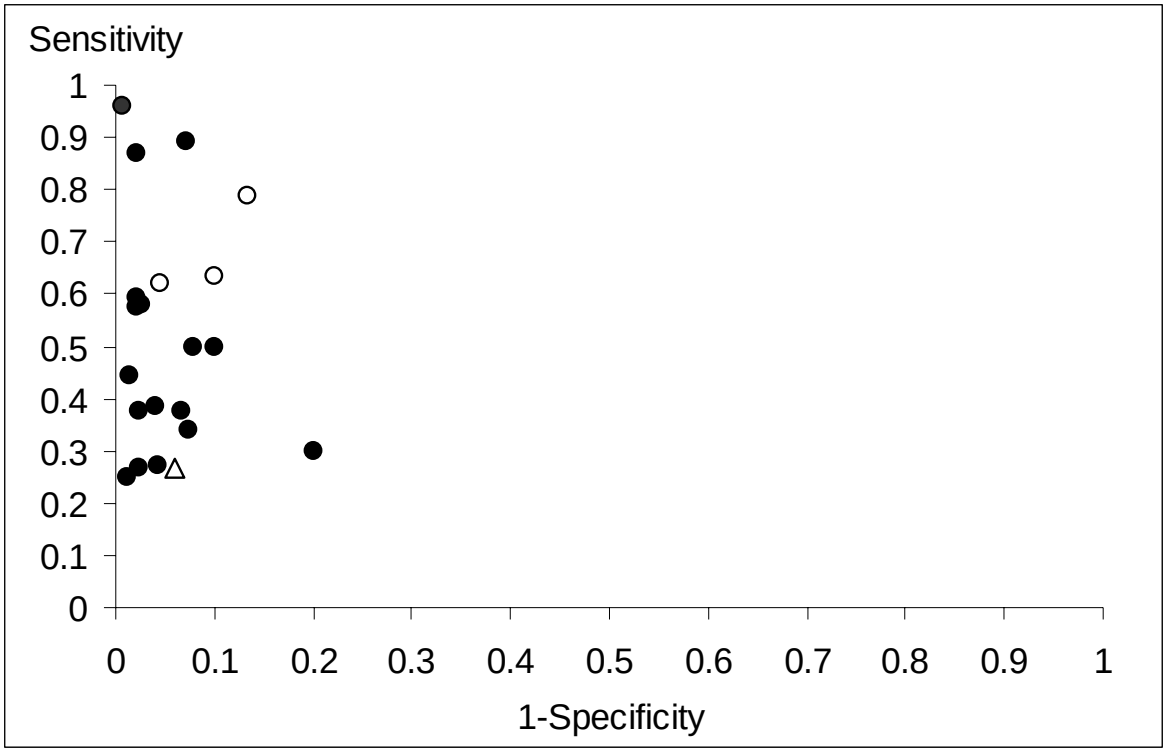
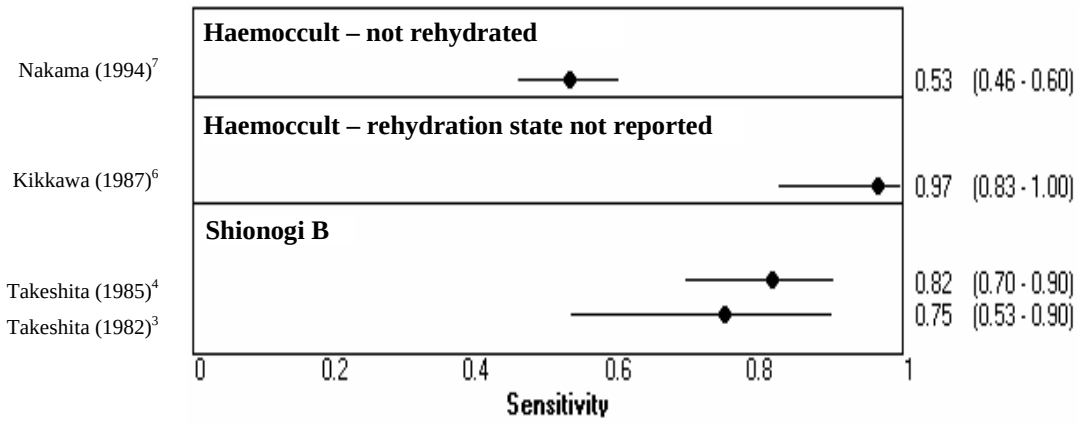


Figure 8: The detection of colorectal cancers using Haemoccult (●), Haemoccult Sensa (○) and Shionogi B (△) based on the results of the diagnostic cohort studies

Four diagnostic case-control studies evaluated the diagnostic accuracy of guaiac FOBTs for the detection of CRC. Two evaluated Haemoccult[6, 7] and two evaluated Shionogi B.[3, 4] One study reported using colonoscopy and barium enema to diagnose disease in cases and upper and lower tract endoscopy to verify the disease-free status of controls.[7] the other three studies did not report the reference standards used.[3, 4, 6]

The sensitivity of the Haemoccult test was reported as 95.2% in one study,[6] which was comparable with the highest value reported in a cohort study and 53.0% in the other.[7] The reported specificities, however, were at the lower end of the spectrum, 72.6%[6] and 85.6%.[7] The sensitivity of Shionogi B was reported as being much higher in the case control studies, at 81.7%[4] and 75.0%[3] (when the 'quasipositive' results reported in these studies were classified as positive), compared to the cohort study where sensitivity was 26.8%. The corresponding specificities were 63.3%[4] and 95.0%[3], compared with 94.1% in the cohort study. Even when the 'quasipositive' results were classified as negative, sensitivity of Shionogi B was still much higher in the case control studies, at 69.7%[4] and 70.0%.[3] The corresponding specificities were 79.0%[4] and 97.6%.[3] The main results are presented in figure 9 and 10, and all results are presented in table 1.

Sensitivity



Specificity

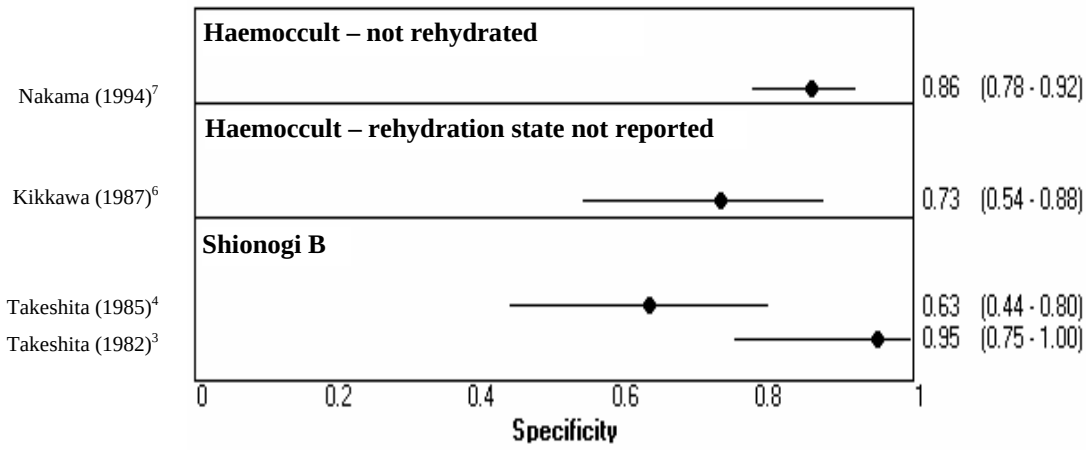


Figure 9: The sensitivity and specificity of guaiac FOBTs for the detection of CRC as reported in diagnostic case-control studies

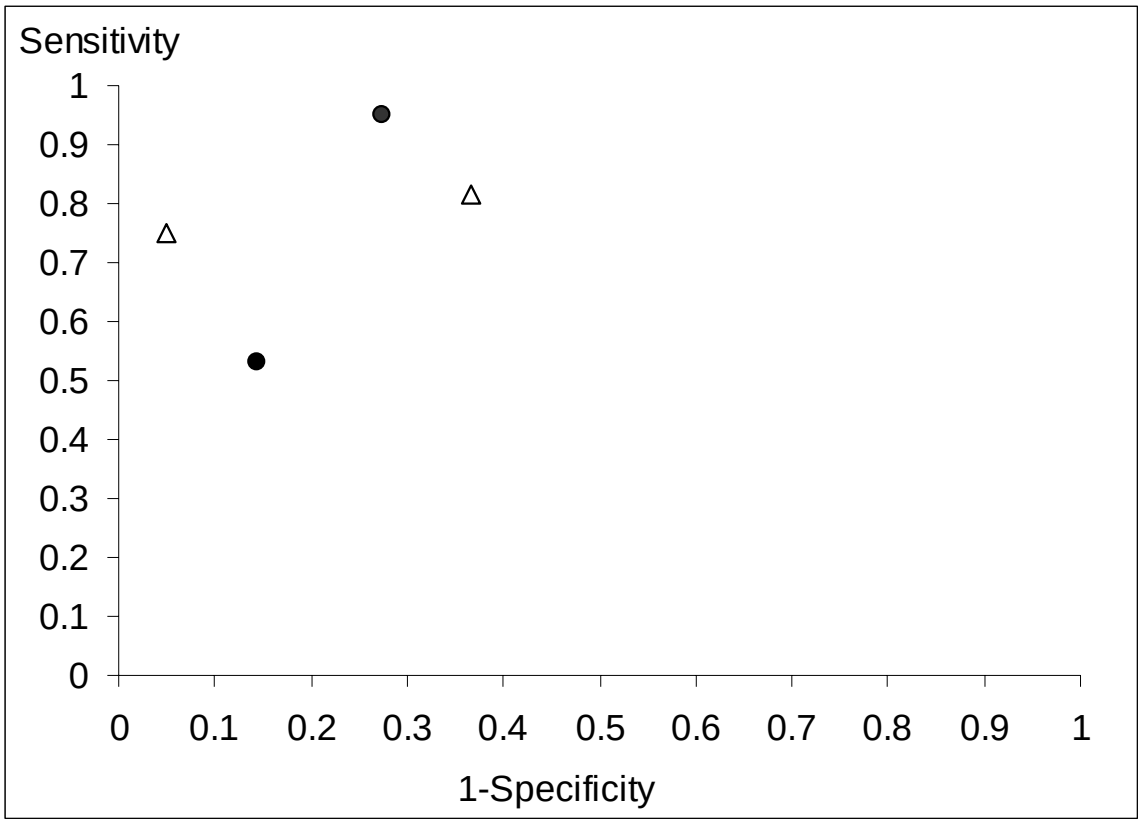


Figure 10: The detection of colorectal cancers using Haemoccult (●) and Shionogi B (△) based on the results of the diagnostic case-control studies

4.2.4 Diagnosis of all adenomas using guaiac FOBTs

All seven diagnostic cohorts that evaluated the diagnostic accuracy of guaiac FOBTs for the detection of all adenomas, used Haemoccult.[64, 65, 67, 70, 80, 97, 113] There were no diagnostic case-control studies evaluating the diagnostic accuracy of guaiac FOBTs to detect all adenomas. The reference standards used for people with a positive FOBT included colonoscopy,[70, 80, 97] colonoscopy and barium enema (in some or all participants),[113] colonoscopy or barium enema,[64, 65] with one study also referring to the cancer registry,[64] or sigmoidoscopy.[67] The reference standards used for people with a negative FOBT included colonoscopy,[80, 97] sigmoidoscopy,[65, 67, 70, 113] or referral to the cancer registry.[64] Five studies recruited an appropriate patient spectrum.[64, 67, 70, 80, 97] There was statistically significant heterogeneity (Cochrane $Q<0.05$ and/or $I^2>75\%$) between studies evaluating Haemoccult, therefore pooling was not undertaken.

For the five studies that examined Haemocult slides that had not been rehydrated, the sensitivity of Haemoccult was low when three consecutive stool were examined, ranging from 5.2% (specificity 98.0%) to 19.1% (specificity 79.7%). Specificity ranged from 79.7% (sensitivity 19.1%) to 98.9% (sensitivity 17.5%).[64, 65, 67, 80, 113] Rehydrated Haemoccult slides were examined in three studies. These also reported low sensitivities, ranging from 9.5% (specificity 93.6%) to 12.9% (specificity 90.5%), and specificities from 90.5% (sensitivity 12.9%) to 93.9% (sensitivity 9.7%).[67, 70, 97] One study compared the accuracy of Haemoccult tests where samples were collected at home for three consecutive days to that of Haemoccult performed using a single stool specimen collected via a digital rectal examination examination (DRE). Sensitivity was reported as very low for both tests, but was slightly better with the home test (Home: 9.7%, DRE: 4.1%), and specificity was slightly better in the DRE test (Home: 93.9%, DRE: 97.5%).[97] The main results are presented in figures 11 and 12, and all results are presented in table 1.

Sensitivity

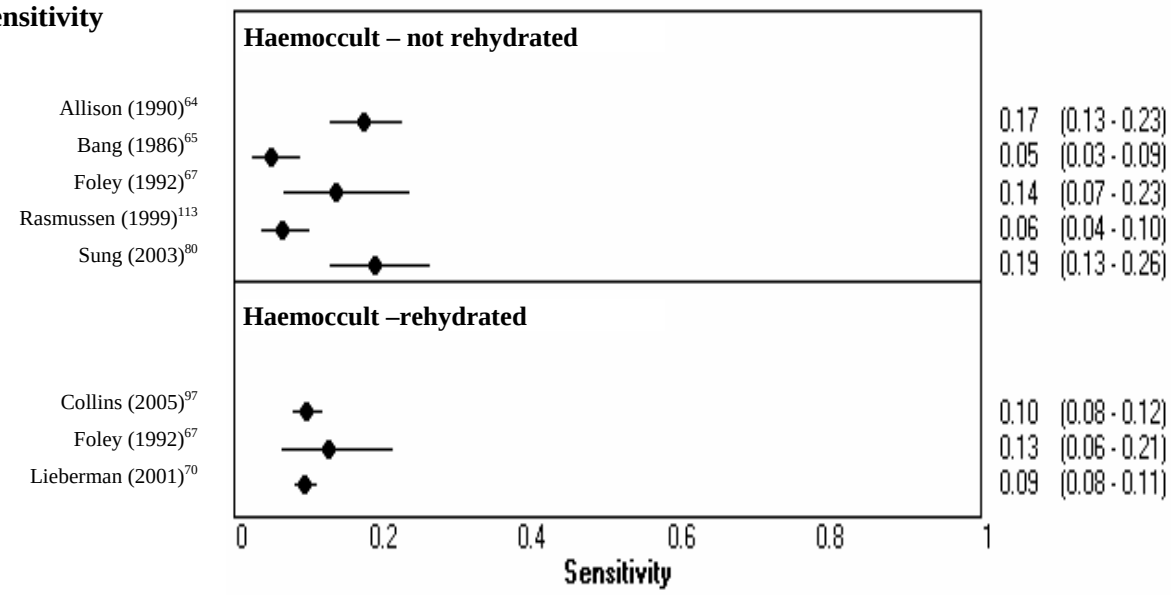


Figure 11a: The sensitivity of guaiac FOBTs for the detection of all adenomas as reported in diagnostic cohort studies

Specificity

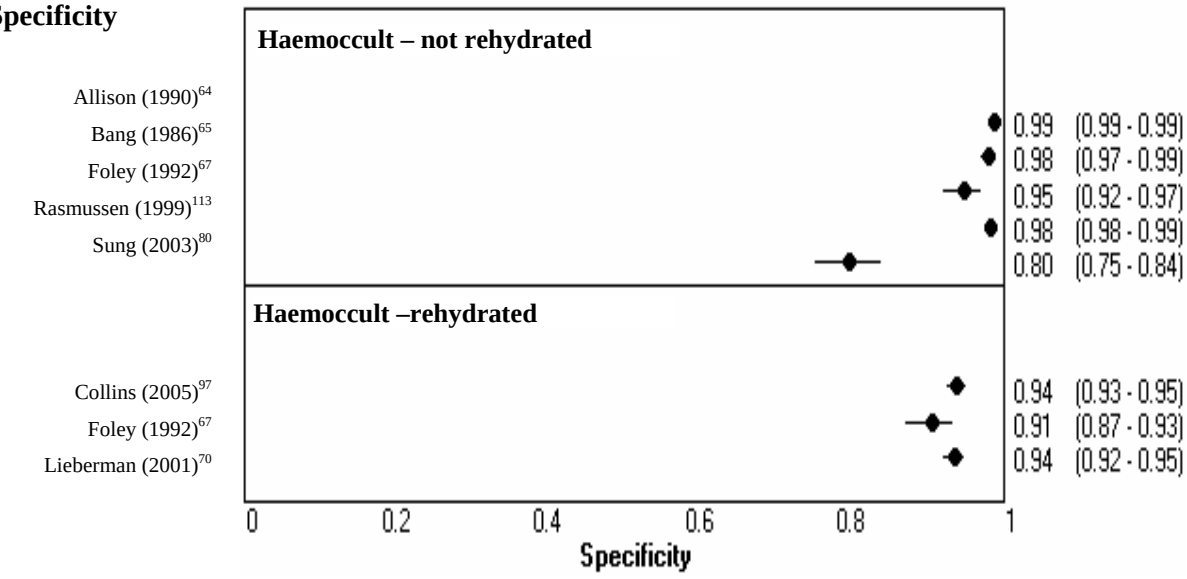


Figure 11b: The specificity of guaiac FOBTs for the detection of all adenomas as reported in diagnostic cohort studies

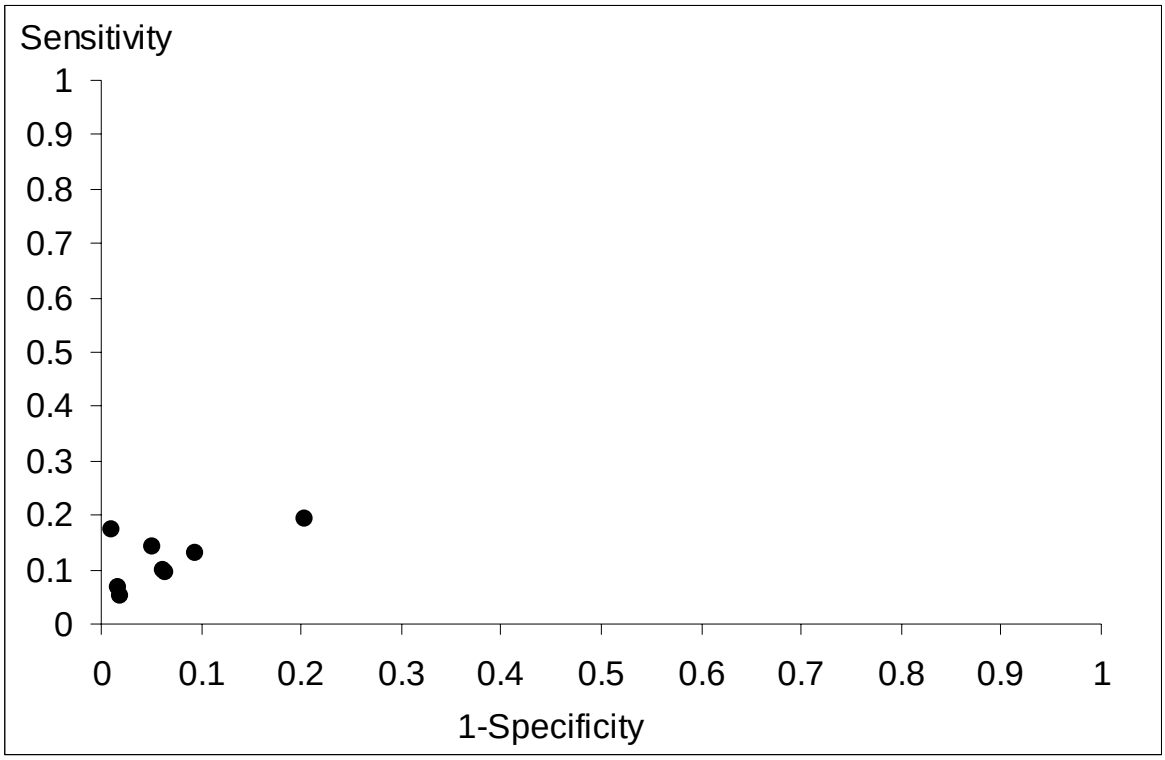


Figure 12: The detection of all adenomas using Haemoccult based on the results of diagnostic cohort studies

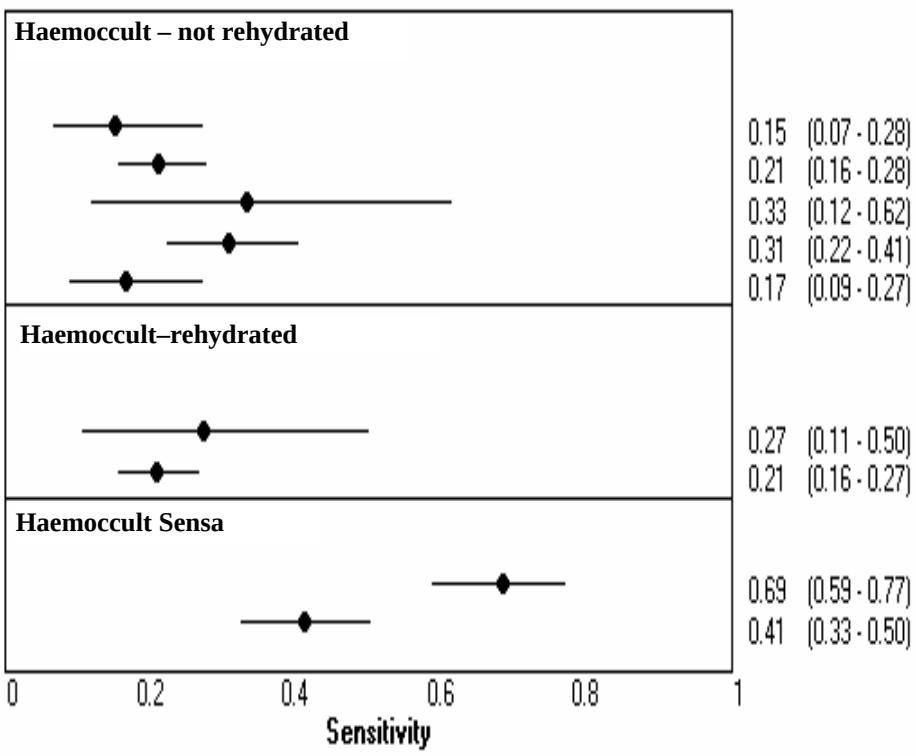
4.2.5 Diagnosis of adenomas 1cm or larger using guaiac FOBTs

Seven diagnostic cohorts evaluated the diagnostic accuracy of guaiac FOBTs for the detection of adenomas of 1cm or larger. Six evaluated Haemoccult[8, 65, 67, 93, 97, 113] and two Haemoccult Sensa.[5, 8] There were no diagnostic case-control studies. The reference standards used for people with a positive FOBT included colonoscopy,[5, 97] colonoscopy and barium enema (in some or all participants),[113] colonoscopy or barium enema,[65] colonoscopy and follow-up,[8] or sigmoidoscopy.[67, 93] The reference standards used for people with a negative FOBT included colonoscopy,[97] sigmoidoscopy,[65, 67, 93, 113] flexible colonoscopy,[5] referral to the cancer registry and follow-up.[8] Only three studies recruited an appropriate patient spectrum.[8, 67, 97] There was statistically significant heterogeneity (Cochrane $Q<0.05$ and/or $I^2>75\%$) between studies evaluating Haemoccult, therefore pooling was not undertaken.

The sensitivity of Haemoccult for the detection of adenomas of 1cm in size or greater (though still low) appeared better than that for all adenomas when three consecutive stool samples were examined. Sensitivity ranged from 15.7% (specificity 98.1%) to 33.3% (specificity 94.5%). Specificity ranged from 90.0% (sensitivity 27.6%) to 99.9% (sensitivity 21.3%).[8, 65, 67, 93, 97, 113] Two studies evaluated rehydrated Haemoccult slides, and reported sensitivities of 27.6% (specificity 90.9%)[67] and 21.0% (specificity 93.8%).[97] Sensitivity ranged from 15.7% (specificity 98.1%) to 33.3% (specificity 94.5%) and specificity from 94.5% (sensitivity 33.3%) to 99.9% (sensitivity 21.3%) for Haemoccult slides that had not been rehydrated.[8, 65, 67, 93, 113] One study compared the accuracy of Haemoccult tests where samples were collected at home for three consecutive days to that of Haemoccult performed using a single stool specimen collected via a digital rectal examination. This study reported that sensitivity was better with the home test (Home: 21.0%, DRE: 4.4%), and specificity was better in the DRE test (Home: 93.8%, DRE: 97.0%).[97]

Haemoccult Sensa was evaluated in two studies, both of which reported this test to be more sensitive, but less specific than Haemoccult. Sensitivity was reported as 68.4% (specificity 87.5%)[8] and 41.3% (specificity 90.6%).[5] The main results are presented in figure 13 and 14, and all results are presented in table 1.

Sensitivity



Specificity

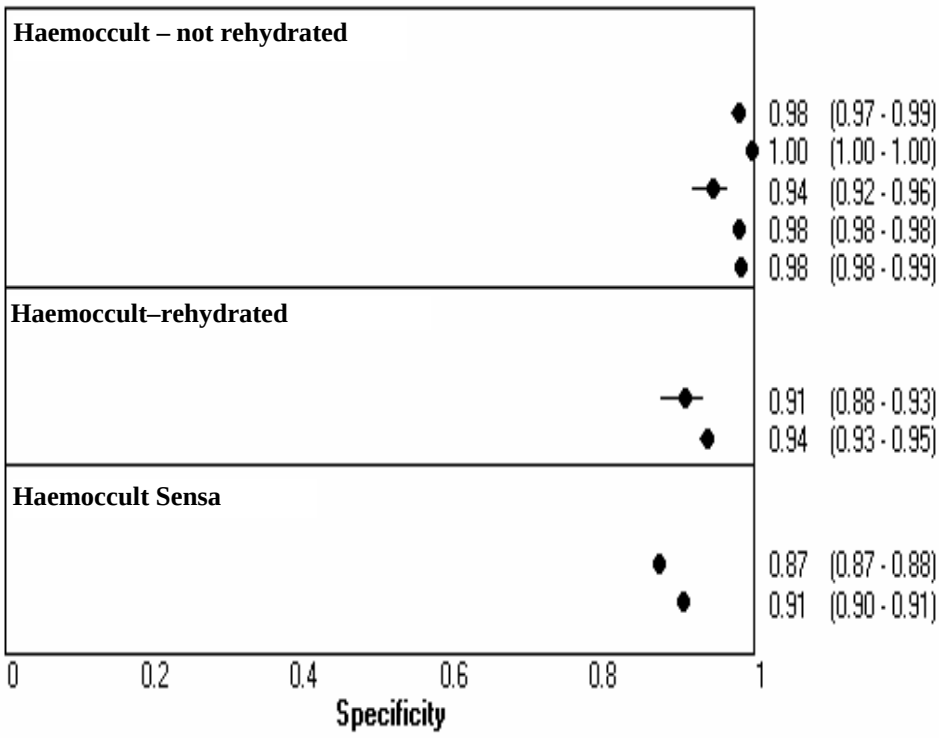


Figure 13: The sensitivity and specificity of guaiac FOBTs for the detection of all adenomas as reported in diagnostic case-control studies

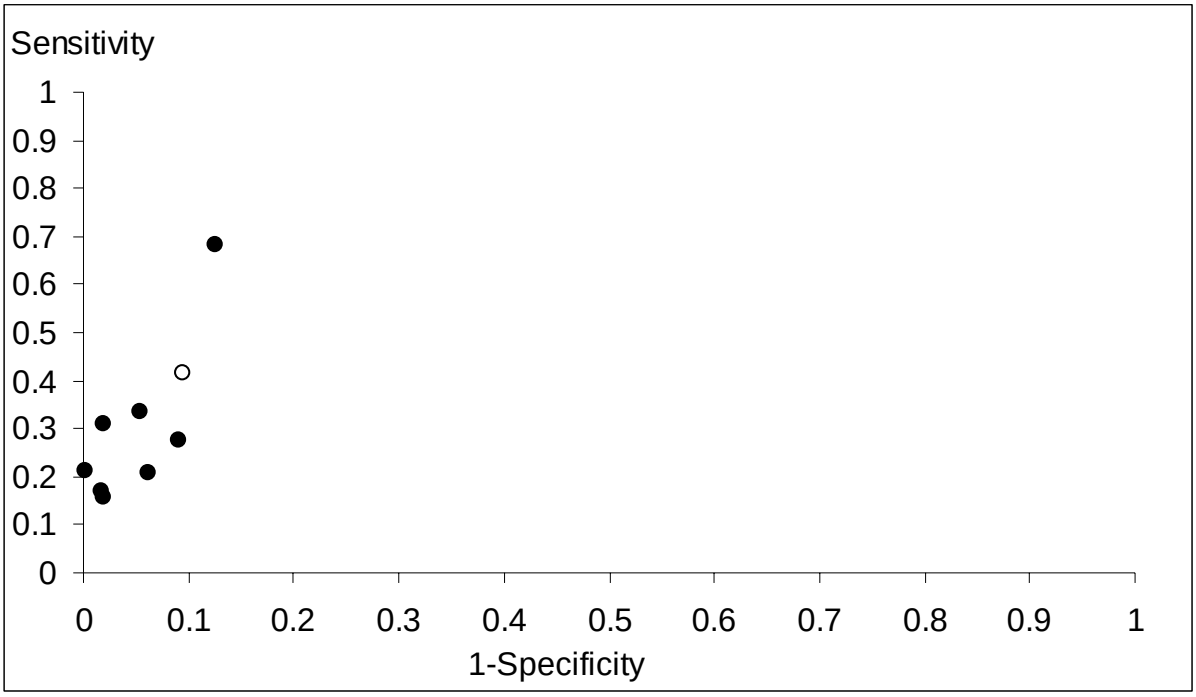


Figure 14: The detection of adenomas of 1cm or larger using Haemoccult (●) and Haemoccult Sensa (○), based on the results of diagnostic cohort studies

Table 1: Results of studies that evaluated guaiac FOBTs

Study ID	Index test†	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
All neoplasms													
Allison (1990)[64]	HO-NR-3 days	Cohort	C or BE/CR	CR	64	125	269	13007	19.3 (15.2, 24.0)	99.0 (98.9, 99.2)	20.21 (15.27, 26.74)	0.81 (0.77, 2.32)	24.81 (17.95, 34.28)
Bang (1986)[65]	HO-NR-3 days	Cohort	C or BE	S	14	24	218	1217	6.2 (3.5, 10.1)	98.0 (97.1, 98.7)	3.15 (1.67, 5.95)	0.96 (0.93, 2.35)	3.30 (1.70, 6.41)
	HO-NR-3 days				11	18	66	341	14.7 (7.7, 24.6)	94.9 (92.0, 96.9)	2.87 (1.43, 5.74)	0.90 (0.82, 0.99)	3.19 (1.46, 6.97)
Foley (1992)[67]	HO-R-3 days	Cohort	S	S	13	33	80	318	14.4 (8.0, 23.1)	90.5 (86.9, 93.3)	1.51 (0.84, 2.72)	0.95 (0.87, 1.04)	1.59 (0.81, 3.14)
	HO-NR and R-3 days				24	51	145	660	14.4 (9.5, 20.6)	92.8 (90.6, 94.6)	1.99 (1.27, 3.13)	0.92 (0.87, 2.29)	2.16 (1.29, 3.61)
Parikh (2001)[77]	HO-NR-3 days	Cohort	C	S	30	17	36	267	45.5 (33.1, 58.2)	94.0 (90.6, 96.5)	7.59 (4.46, 12.92)	0.58 (0.47, 0.73)	13.09 (6.57, 26.08)
	HO-NR-1 DRE				27	20	39	264	41.0 (29.2, 53.7)	92.8 (89.2, 95.5)	5.71 (3.44, 9.47)	0.64 (0.52, 0.78)	8.98 (4.63, 17.42)
Rasmussen (1999)[113]	HO-NR-3 days	Cohort	C/BE	S	23	31	240	1844	8.9 (5.8, 13.0)	98.3 (97.6, 98.9)	5.30 (3.16, 8.90)	0.93 (0.89, 0.96)	5.72 (3.30, 9.93)
Ribet (1980)[78]	HO-NR-3 days	Cohort	C/BE/S	S/BE	5	22	30	173	15.3 (5.5, 31.2)	88.5 (83.2, 92.6)	1.33 (0.56, 3.15)	0.96 (0.83, 1.11)	1.39 (0.51, 3.81)
Sung (2003)[80]	HO-NR-3 days	Cohort	C	C	29	72	123	281	19.3 (13.4, 26.4)	79.5 (74.9, 83.6)	0.94 (0.64, 1.38)	1.02 (0.92, 1.12)	0.93 (0.58, 1.50)
Collins (2005)[97]	HO-R-3 days	Cohort	C	C	114	101	895	1555	11.3 (9.4, 13.5)	93.9 (92.6, 95.0)	1.85 (1.43, 2.39)	0.94 (0.92, 2.36)	1.96 (1.48, 2.59)
	HO-R-1 DRE	Cohort	C	C	43	41	966	1615	4.3 (3.1, 5.7)	97.5 (96.6, 98.2)	1.72 (1.13, 2.61)	0.98 (0.97, 2.37)	1.75 (1.14, 2.70)
Lieberman (2001)[70]	HO-R-3 days	Cohort	C	S	150	89	1322	1314	10.2 (8.7, 11.9)	93.6 (92.2, 94.8)	1.60 (1.25, 2.06)	0.96 (0.94, 0.98)	1.67 (1.27, 2.20)
Bhattacharya (1997)[81]	HO-NS-UC	Case-control	C	C	36	84	36	84	50.0 (38.0, 62.0)	50.0 (42.2, 57.8)	1.00 (0.76, 1.32)	1.00 (0.76, 1.32)	1.00 (0.58, 1.73)
Miyoshi (1992)[9]	HO-NS-3 days	Case-control	C	C and/ or BE	33	11	13	22	71.3 (56.5, 84.0)	66.2 (48.2, 82.0)	2.11 (1.27, 3.49)	0.43 (0.26, 0.72)	4.86 (1.88, 12.56)
St John (1992)[79]	HO-NS-3 days	Case-control	C	C	137	1	73	149	65.2 (58.4, 71.7)	99.0 (96.3, 100)	65.60 (13.31, 323.43)	0.35 (0.29, 0.42)	186.45 (36.42, 954.54)
Allison (2002)[5]	HO Sensa	Cohort	C	C	59	525	78	5137	43.1 (34.6, 51.8)	90.7 (89.9, 91.5)	4.65 (3.77, 5.72)	0.63 (0.54, 0.73)	7.41 (5.23, 10.50)
St John (1993)[10]	HO Sensa	Case-control	C	NR	136	0	52	50	72.2 (65.4, 78.6)	99.0 (92.9, 100)	73.67 (4.66, 1163.50)	0.28 (0.22, 0.35)	262.60 (15.91, 4334.10)
Klug (1983)[68]	KryptoHaem	Cohort	S	S	17	12	3	758	83.3 (62.1, 96.8)	98.4 (97.3, 99.2)	51.40 (28.72, 92.00)	0.17 (0.07, 0.44)	303.40 (84.65, 1087.40)
Lampe (1982)[83]	KryptoHaem	Case-control	NR	NR	73	4	81	253	47.4 (39.3, 55.6)	98.3 (96.1, 99.6)	27.19 (10.72, 68.96)	0.54 (0.46, 0.62)	50.80 (18.99, 135.90)

Study ID	Index test†	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Miyoshi (1992)[9]	Shionogi B	Case-control	C	C and/or BE	34	13	12	20	73.4 (58.9, 85.7)	60.3 (42.1, 77.1)	1.85 (1.18, 2.90)	0.44 (0.26, 0.76)	4.19 (1.63, 10.77)
Matsuse (1989)[2]	Unspecified	Case-control	C/BE	C and/or BE	26	13	18	33	59.1 (43.2, 73.7)	71.7 (56.5, 84.0)	2.09 (1.24, 3.52)	0.57 (0.38, 0.85)	3.67 (1.52, 8.83)
Miyoshi (1988)[1]	Unspecified	Case-control	NR	NR	27	8	17	20	61.4 (45.5, 75.6)	71.4 (51.3, 86.8)	2.15 (1.14, 4.04)	0.54 (0.35, 0.84)	3.97 (1.43, 11.01)
CRC													
Allison (1990)[64]	HO-NR-3 days	Cohort	C or BE	CR	21	168	64	13212	25.0 (16.0, 35.3)	98.7 (98.5, 98.9)	19.85 (13.37, 29.49)	0.76 (0.67, 0.86)	26.14 (15.68, 43.58)
Allison (1996)[8]	HO-NR-3 days	Cohort	C/FU	CR/FU	13	185	22	7845	37.5 (21.5, 55.1)	97.7 (97.3, 98.0)	16.24 (10.40, 25.34)	0.64 (0.50, 0.82)	25.38 (12.73, 50.61)
Bang (1986)[65]	HO-NR-3 days	Cohort	C or BE	S	3	35	9	1426	26.9 (5.5, 57.2)	97.6 (96.7, 98.3)	11.09 (4.28, 28.75)	0.75 (0.54, 1.04)	14.80 (4.16, 52.72)
Bennett (1996)[93]	HO-NR-UC	Cohort	S	S	11	43	14	2841	44.2 (25.0, 64.9)	98.5 (98.0, 98.9)	29.34 (17.39, 49.48)	0.57 (0.40, 0.80)	51.81 (22.59, 118.79)
Castiglione (1991)[94]	HO-NR-3 days	Cohort	S	CR/RS	25	328	17	14622	59.3 (43.3, 74.4)	97.8 (97.6, 98.0)	26.99 (20.61, 35.35)	0.42 (0.29, 0.60)	64.86 (34.96, 120.35)
	HO-NR-3 days				1	28	2	405	37.5 (2.8, 87.7)	93.4 (90.7, 95.6)	5.71 (1.54, 21.25)	0.67 (0.31, 1.43)	8.54 (1.09, 66.95)
Foley (1992)[67]	HO-R-3 days	Cohort	S	S	2	44	2	396	50.0 (9.4, 90.6)	89.9 (86.7, 92.6)	4.96 (1.98, 12.43)	0.56 (0.23, 1.34)	8.91 (1.50, 52.85)
	HO-NR and R combined				3	72	5	800	38.9 (8.5, 75.5)	91.7 (89.7, 93.5)	4.68 (2.01, 10.94)	0.67 (0.40, 1.12)	7.03 (1.80, 27.42)
Launoy (1997)[69]	HO-NR-UC	Cohort	C	CR	131	1855	95	67729	57.9 (51.2, 64.5)	97.3 (97.4, 97.2)	21.72 (19.28, 24.49)	0.43 (0.37, 0.50)	50.26 (38.46, 65.68)
Michalek (1988)[100]	HO-NR-3 days	Cohort	GP/Q/CR	CR	16	248	2	11231	86.8 (65.3, 98.6)	97.8 (97.6, 98.1)	40.12 (32.39, 49.69)	0.13 (0.04, 0.43)	298.30 (78.41, 1134.80)
Niv (2002)[112]	HO-NR-3 days	Cohort	C	CR	13	89	21	2145	38.6 (22.2, 56.4)	96.0 (95.1, 96.8)	9.63 (6.05, 15.33)	0.64 (0.49, 0.83)	15.05 (7.38, 30.70)
Rasmussen (1999)[113]	HO-NR-3 days	Cohort	C/BE	S	7	47	5	2079	57.7 (27.7, 84.8)	97.8 (97.1, 98.4)	25.83 (15.00, 44.50)	0.43 (0.23, 0.82)	59.70 (19.15, 186.15)
Sung (2003)[80]	HO-NR-3 days	Cohort	C	C	1	100	3	401	30.0 (0.6, 80.6)	80.0 (76.3, 83.5)	1.50 (0.39, 5.78)	0.88 (0.49, 1.56)	1.71 (0.25, 11.74)
Winawer (1980)[106]	HO-NR-3 days	Cohort	S/BE	S	12	43	0	5394	96.2 (73.5, 100)	99.2 (98.9, 99.4)	120.20 (87.70, 164.76)	0.04 (0, 0.59)	3100.29 (180.70, 53191.90)
Nakama (1994)[7]	HO-NR-1 day	Case-control	C/BE	ULTE	106	14	94	86	53.0 (45.8, 60.1)	85.6 (77.6, 92.1)	3.69 (2.25, 6.05)	0.55 (0.46, 0.65)	6.72 (3.61, 12.51)
Brevinge (1997)[107]	HO-R-3 days	Cohort	S/BE	S	6	35	17	767	27.1 (10.2, 48.4)	95.6 (94.0, 96.9)	6.13 (2.95, 12.73)	0.76 (0.60, 0.97)	8.03 (3.07, 21.00)

Study ID	Index test†	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Collins (2005)[97]	HO-R-3 days	Cohort	C	C	23	192	45	2405	34.1 (22.8, 46.3)	92.6 (91.5, 93.6)	4.60 (3.22, 6.56)	0.71 (0.60, 0.84)	6.45 (3.84, 10.85)
	HO-R-1 DRE				5	79	63	2518	8.0 (2.4, 16.3)	96.9 (96.2, 97.6)	2.60 (1.14, 5.98)	0.95 (0.89, 1.02)	2.74 (1.12, 6.74)
Lieberman (2001)[70]	HO-R-3 days	Cohort	C	S	12	227	12	2634	50.0 (29.1, 70.9)	92.1 (91.0, 93.0)	6.29 (4.17, 9.49)	0.54 (0.37, 0.80)	11.58 (5.23, 25.66)
Mandel (1989)[110]	HO-R-3 days	Cohort	C/BE	Q	183	7047	22	89953	89.1 (84.2, 93.2)	92.7 (92.9, 92.6)	12.26 (11.63, 12.93)	0.12 (0.08, 0.17)	104.10 (67.15, 161.38)
Kikkawa (1987)[6]	HO-NS-1 day	Case-control	NR	NR	25	3	5	27	83.3 (65.3, 94.4)	90.0 (73.5, 97.9)	8.33 (2.82, 24.67)	0.19 (0.08, 0.416)	45.00 (9.73, 208.08)
	HO-NS-2 days				28	5	2	25	93.3 (77.9, 99.2)	83.3 (65.3, 94.4)	5.60 (2.50, 12.536)	0.08 (0.02, 0.31)	70.00 (12.46, 393.36)
	HO-NS-3 days				29	8	1	22	95.2 (82.8, 99.9)	72.6 (54.1, 87.7)	3.47 (1.95, 6.19)	0.07 (0.01, 0.32)	52.06 (8.43, 321.43)
Allison (1996)[8]	HO Sensa	Cohort	C/FU	CR/FU	27	1046	7	6824	78.6 (62.1, 91.3)	86.7 (85.9, 87.5)	5.91 (4.93, 7.09)	0.25 (0.13, 0.47)	23.91 (10.64, 53.75)
Allison (2002)[5]	HO Sensa	Cohort	C	C	9	575	5	5210	63.3 (35.1, 87.2)	90.1 (89.3, 90.8)	6.37 (4.30, 9.43)	0.41 (0.21, 0.79)	15.64 (5.45, 44.85)
Rennert (2001)[105]	HO Sensa	Cohort	C	CR/RS	48	987	29	21129	62.2 (50.6, 73.1)	95.5 (95.3, 95.8)	13.93 (11.59, 16.73)	0.40 (0.30, 0.53)	35.18 (22.16, 55.84)
Murakami (1992)[72]	Shionogi B	Cohort	CR	CR	7	201	20	3221	26.8 (11.1, 46.3)	94.1 (93.3, 94.9)	4.55 (2.43, 8.52)	0.78 (0.62, 0.97)	5.85 (2.50, 13.66)
Takeshita (1985)[4]	Shionogi B 'quasipositives' classified as positive	Case-control	NR	NR	49	11	11	19	81.7 (69.6, 90.5)	63.3 (43.9, 80.1)	2.23 (1.37, 3.62)	0.29 (0.16, 0.53)	7.69 (2.86, 20.70)
	Shionogi B 'quasipositives' classified as negative				42	6	18	24	69.7 (56.8, 81.2)	79.0 (61.4, 92.3)	3.32 (1.65, 6.71)	0.38 (0.25, 0.59)	8.66 (3.11, 24.08)
Takeshita (1982)[3]	Shionogi B 'quasipositives' classified as positive	Case-control	NR	NR	18	1	6	19	75.0 (53.3, 90.2)	95.0 (75.1, 99.9)	15.00 (2.19, 102.75)	0.26 (0.31, 0.53)	57.00 (6.23, 521.15)
	Shionogi B 'quasipositives' classified as negative				17	0	7	20	70.0 (48.9, 87.4)	97.6 (83.2, 100)	29.40 (1.88, 460.18)	0.31 (0.17, 0.56)	95.67 (5.09, 1796.9)

All adenomas													
Allison (1990)[64]	HO-NR-3 days	Cohort	C/BE/CR	CR	43	146	205	13071	17.5 (12.8, 22.6)	98.9 (98.7, 99.1)	15.76 (11.51, 21.58)	0.83 (0.79, 0.88)	18.89 (13.11, 27.22)
Bang (1986)[65]	HO-NR-3 days	Cohort	C or BE	S	11	24	209	1217	5.2 (2.5, 8.8)	98.0 (97.1, 98.8)	2.64 (1.33, 5.24)	0.97 (0.94, 1.00)	2.73 (1.33, 5.58)
	HO-NR-3 days				10	18	64	341	14.0 (7.1, 23.9)	94.9 (92.0, 96.9)	2.72 (1.33, 5.57)	0.91 (0.83, 1.00)	3.01 (1.35, 6.71)
Foley (1992)[67]	HO-R-3 days	Cohort	S	S	11	33	77	318	12.9 (6.7, 21.7)	90.5 (86.9, 93.3)	1.36 (0.72, 2.55)	0.96 (0.88, 1.05)	1.41 (0.69, 2.88)
	HO- NR and R -3 days				21	51	141	659	13.2 (8.2, 19.1)	92.8 (90.7, 94.6)	1.82 (1.13, 2.92)	0.94 (0.88, 1.00)	1.95 (1.14, 3.32)
Rasmussen (1999)[113]	HO-NR-3 days	Cohort	C/BE	S	16	31	235	1844	6.5 (3.7, 10.1)	98.3 (97.7, 98.9)	3.90 (2.18, 6.97)	0.95 (0.92, 0.98)	4.10 (2.23, 7.56)
Sung (2003)[80]	HO-NR-3 days	Cohort	C	C	28	72	120	284	19.1 (13.0, 26.2)	79.7 (75.2, 83.8)	0.94 (0.64, 1.39)	1.01 (0.92, 1.12)	0.93 (0.57, 1.50)
Collins (2005)[97]	HO-R-3 days	Cohort	C	C	91	101	850	1555	9.7 (7.9, 11.7)	93.9 (92.6, 95.0)	1.59 (1.21, 2.08)	0.96 (0.94, 0.99)	1.65 (1.23, 2.21)
	HO-R-1 DRE				38	41	903	1615	4.1 (2.9, 5.5)	97.5 (96.7, 98.2)	1.63 (1.06, 2.51)	0.98 (0.97, 1.00)	1.66 (1.06, 2.59)
Lieberman (2001)[70]	HO-R-3 days	Cohort	C	S	138	89	1320	1314	9.5 (8.0, 11.1)	93.6 (92.3, 94.9)	1.49 (1.15, 1.92)	0.97 (0.95, 0.99)	1.54 (1.17, 2.03)
Adenomas >1cm													
Bang (1986)[65]	HO-NR-3 days	Cohort	C or BE	S	8	27	45	1381	15.7 (6.7, 27.6)	98.0 (97.2, 98.7)	8.06 (3.93, 16.56)	0.86 (0.77, 0.97)	9.38 (4.12, 21.39)
Bennett (1996)[93]	HO-NR-UC	Cohort	S	S	40	3	149	2692	21.3 (15.7, 27.8)	99.9 (99.6, 100)	164.19 (55.65, 484.47)	0.79 (0.73, 0.85)	208.40 (69.07, 628.79)
	HO-NR-3 days				5	23	10	395	33.3 (11.8, 61.6)	94.5 (91.9, 96.5)	6.06 (2.67, 13.74)	0.71 (0.50, 1.01)	8.59 (2.71, 27.20)
Foley (1992)[67]	HO-R-3 days	Cohort	S	S	6	38	16	379	27.6 (10.7, 50.2)	90.9 (90.6, 96.5)	2.99 (1.42, 6.32)	0.80 (0.62, 1.04)	3.74 (1.38, 10.12)
	HO-NR and R combined				11	61	26	774	30.3 (15.9, 47.0)	92.6 (90.7, 94.4)	4.11 (2.40, 7.05)	0.75 (0.61, 0.93)	5.47 (2.61, 11.45)
Allison (1996)[8]	HO-NR-3 days	Cohort	C/FU	CR/FU	33	152	74	7771	31.0 (22.3, 40.5)	98.1 (97.8, 98.4)	16.12 (11.68, 22.24)	0.70 (0.62, 0.80)	22.92 (14.79, 35.51)
Rasmussen (1999)[113]	HO-NR-3 days	Cohort	C/BE	S	12	35	60	2019	17.1 (8.9, 27.3)	98.3 (97.6, 98.8)	9.91 (5.44, 18.08)	0.84 (0.76, 0.94)	11.75 (5.88, 23.52)
Collins (2005)[97]	HO-R-3 days	Cohort	C	C	45	147	171	2234	21.0 (15.6, 26.9)	93.8 (92.8, 94.8)	3.39 (2.50, 4.58)	0.84 (0.79, 0.90)	4.02 (2.79, 5.80)
	HO-R-1 DRE				9	70	207	2311	4.4 (1.9, 7.8)	97.0 (96.3, 97.7)	1.48 (0.76, 2.87)	0.99 (0.96, 1.02)	1.50 (0.75, 3.00)
Allison (1996)[8]	HO Sensa	Cohort	C/FU	CR/FU	72	974	33	6791	68.4 (58.8, 77.3)	87.5 (86.7, 88.2)	5.45 (4.73, 6.28)	0.36 (0.27, 0.48)	15.08 (9.96, 22.84)
Allison (2002)[5]	HO Sensa	Cohort	C	S	52	532	74	5141	41.3 (32.6, 50.4)	90.6 (89.8, 91.4)	4.40 (3.53, 5.50)	0.65 (0.56, 0.75)	6.80 (4.73, 9.79)

LR+: Positive likelihood ratio; LR-: negative likelihood ratio; DOR: diagnostic odds ratio.

†Indext test: HO: Haemoccult, NR: Not rehydrated, R: rehydrated, NS: rehydration status not specified, 3 days: sampling on three consecutive stool, 1 DRE: sampling from a single digital rectal examination.

*Reference standards include C: colonoscopy, BE: barium enema, S: sigmoidoscopy, FU: follow-up, CR: referral to a cancer registry, RS: resecreening, ULTE: upper and lower tract endoscopy, Q: questionnaire, GP: contact with the general practitioner, singly or in combination, or NR: not reported.

4.3 Immunochemical FOBTs

Twenty immunochemical FOBTs were evaluated in the included studies, Checkmate Hemo, Feca-EIA, Hemo-EIA, Stick-EIA, FlexSure, HemeSelect, Immudia HemSp, Imdia HemSp, Magstream HemSp, RPHA, Iatro Hemcheck, LA Hemochaser, MonoHaem, OC Hemodia, OC Hemocatch, OC Light, LAT, HB Latex, Ouchterlony and the SPA test. HemeSelect, Immudia HemSp, Imdia HemSp, Magstream HemSp, and RPHA were grouped together, and are referred to as Immudia HemSp. OC Hemodia, OC Hemocatch, OC Light, LAT and HB Latex were grouped together and are refered to as OC Light. One study reported the results for three Elisa immune-essay (EIA) FOBTs, Feca-EIA, Hemo-EIA and Stick-EIA.[1] As Feca-EIA was utilised in the other studies evaluating this type of FOBT, the Feca-EIA results were used for comparison in the ROC and forest plots, with the results for the other EIA-FOBTs presented in the table and discussed in the text. The number of participants ranged from 44 to 62,611. The proportion of males was not reported in 21 studies, but where reported, it ranged from 40.8% to 86.1%. Twenty eight studies did not report a mean age of the participants. Of those that did, the mean age ranged from 47 to 53 years. Where a mean age was not reported, only nine studies reported the age range of the participants. The youngest participants included were 13 years in the control group of a diagnostic case control trial, and 30 years in a diagnostic cohort study. The oldest participants were were 89 years in the case group of a diagnostic case control trial, and 80+ years in a diagnostic cohort study.

4.3.1 Quality

Of the 35 included studies that evaluated the diagnostic accuracy of immunochemical FOBTs, 6 were diagnostic cohorts,[66, 71, 73-76] 18 diagnostic case-control studies,[1-4, 6, 7, 9, 10, 42, 82, 85-92] and 11 were either screening trials or RCTs from which cohorts were derived.[5, 8, 46, 95, 96, 98, 99, 101-103,108] Figure 15 shows the proportion of studies that answered "yes", "no" or "unclear" to each of the 13 QUADAS items. Seventy two percent of studies fulfilled the criteria for avoidance of partial verification bias and 58% for avoidance of differential verification bias. Only 3% of studies reported sufficient details on clinical review bias, and diagnostic review bias was avoided in 44% of studies and test review bias in 14%. Twenty seven percent of studies included an appropriate spectrum of patients, and 36% adequately described the selection criteria. Twenty eight percent reported sufficient details on how the reference standard was performed, and 47% on how the index test was performed, to permit replication. Study withdrawals and handling of uninterpretable results were reported in less than 75% and 81% of studies, respectively.

The reference standards used, where reported, varied considerably across the studies, with colonoscopy, barium enema, or sigmoidoscopy used individually or in combination for people with a positive FOBT or cases, and colonoscopy (with or without upper gastrointestinal endoscopy), barium enema, sigmoidoscopy cancer registry, follow-up, health insurance claims, or re-screening individuall or in combination for people with a negative FOBT or controls.

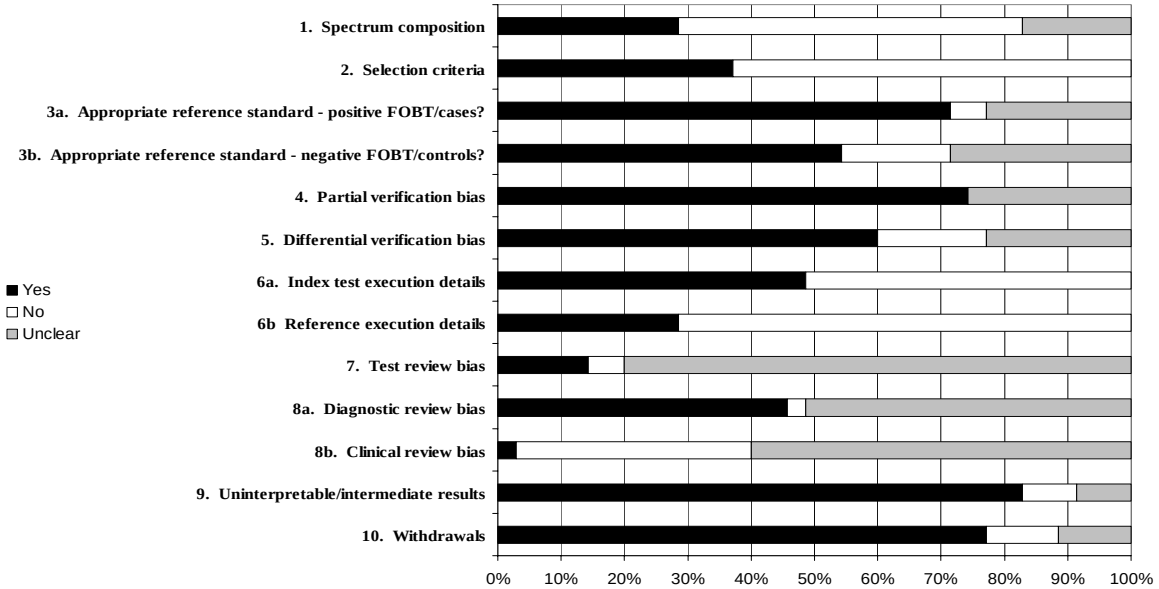


Figure 15: Proportion of immunochemical FOBT studies rated as yes, no, or unclear for each of the QUADAS items

4.3.2 Diagnosis of all neoplasms using immunochemical FOBTs

Six diagnostic cohort studies evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of all neoplasms. Two evaluated Flexsure,[5, 108] two OC Light,[71, 96] one Immudia HemSp,[73] and one the SPA test.[46] The reference standards used for people with a positive FOBT included colonoscopy,[5, 71, 73, 96, 108] or sigmoidoscopy.[46] The reference standards used for people with a negative FOBT included colonoscopy,[71, 73, 96] flexible colonoscopy,[5] or sigmoidoscopy.[46, 108] Four cohort studies recruited an appropriate patient spectrum.[71, 73, 96, 108] Two studies did not name the immunochemical FOBT used and therefore results are presented in the tables, but not included in the synthesis.[66, 101]

The study evaluating Immudia Hemsp reported the highest sensitivity of these studies, 62.6% (specificity 94.3%).[73] The two studies evaluating Flexsure reported sensitivities of 33.2% (specificity 97.5%)[5] and 14.3% (specificity 96.3%).[108] The two studies evaluating OC Light reported sensitivities of 5.4% (specificity 98.5%)[71] and 18.4% (specificity 91.6%).[96] The SPA test was reported as having a sensitivity of 30.3% and the lowest specificity of the studies in this group, 89.4%.[46] The main results are presented in figures 16 and 17, and all results are presented in table 2.

Sensitivity

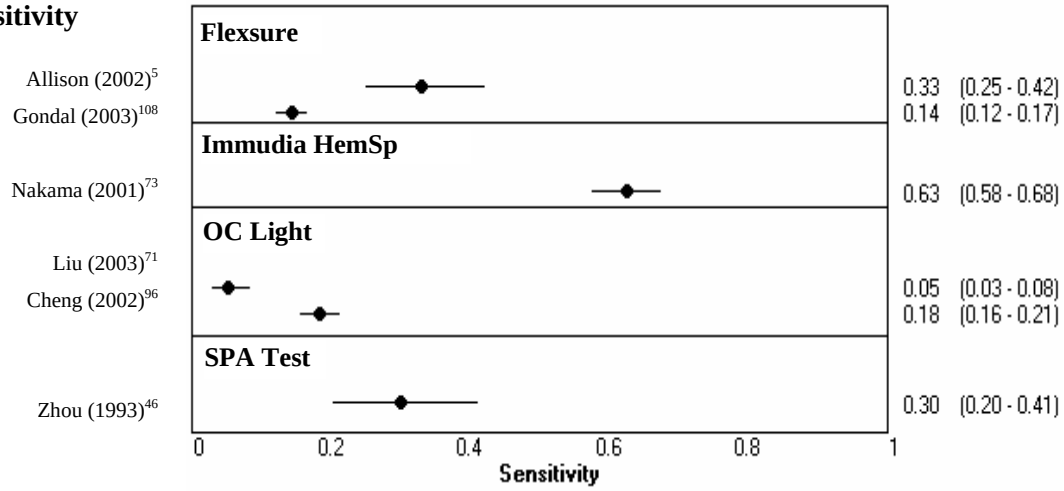


Figure 16a: The sensitivity of immunochemical FOBTs for the detection of all neoplasms as reported in diagnostic cohort studies

Specificity

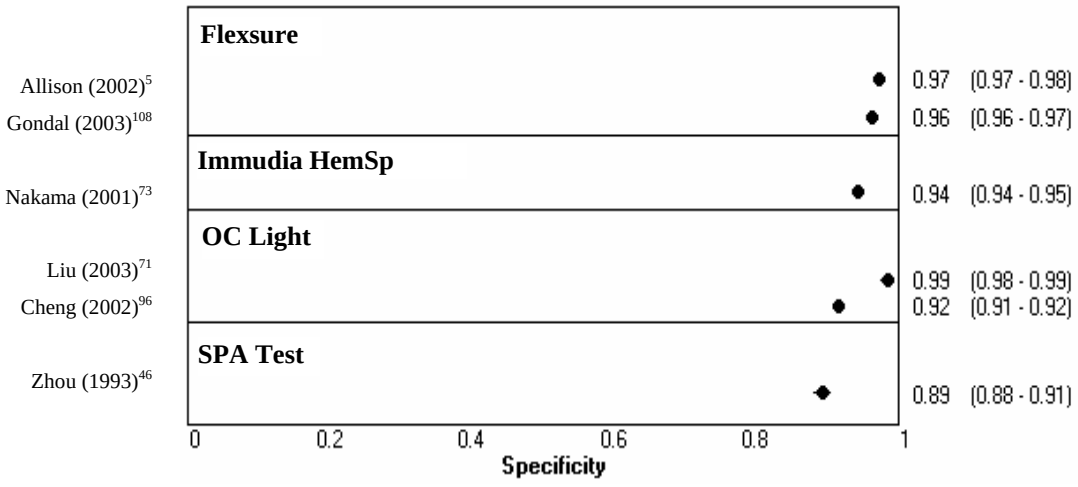


Figure 16b: The specificity of immunochemical FOBTs for the detection of all neoplasms as reported in diagnostic cohort studies

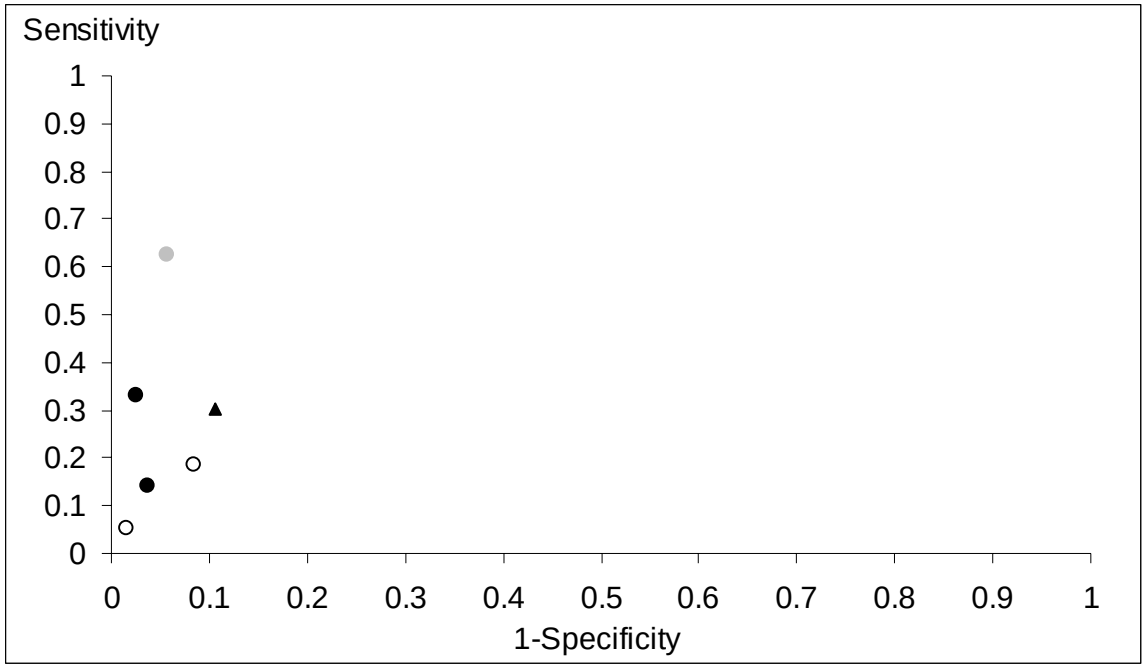


Figure 17: The detection of all neoplasms using Flexsure (●), OC Light (○), Immudia HemSp (◌), and the SPA test (▲), based on the results of the diagnostic cohort studies

Eleven diagnostic case-control studies evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of all neoplasms. Four evaluated EIA-FOBTs,[1, 2, 9, 88] five Immudia HemSp,[1, 2, 10, 91, 92] five OC Light,[1, 2, 86, 88, 89] two MonoHaem,[1, 82] one Iatro Hemcheck,[89] one LA Hemochaser[2] and one the SPA test.[46] The reference standards used to diagnose disease in cases included colonoscopy,[9, 10, 86] colonoscopy and barium enema,[2, 82, 88] or sigmoidoscopy.[46] The reference standards used to verify the disease-free status of controls included colonoscopy,[86] colonoscopy and/or barium enema,[2, 9, 82, 88] or sigmoidoscopy.[46] The reference standard was not reported for either cases or controls in four studies,[1, 89, 91, 92] and was reported for cases only in one study.[10] No diagnostic case control study was deemed to have an appropriate patient spectrum. There was statistically significant between study heterogeneity (Cochrane $Q<0.05$ and/or $I^2>75\%$) in all test groups, therefore pooling was not undertaken.

Overall, the sensitivity of immunochemical FOBTs for the detection of all neoplasms ranged from 25.6% (MonoHaem, specificity 98.3%) to 97.7% (Immudia HemSp, specificity 98.8%), and specificity from 77.0% (Immudia HemSp, sensitivity 54.7%) to 99.0% (Immudia HemSp, sensitivity 80.2% and 87.5%). Immudia HemSp appeared to be the most accurate test in this group, with sensitivity ranging from 43.3% (specificity 79.2%) to 97.7% (specificity 98.8%) and specificity from 77.0% (sensitivity 54.7%) to 99.0% (sensitivity 80.2% and 87.5%). The sensitivity of the EIA-FOBTs ranged from 32.2% (Feca-EIA, specificity 91.4%) to 72.2% (Stick-EIA, specificity 91.9%) and specificity ranged from 81.9% (Feca-EIA, sensitivity 65.6%) to 98.3% (Hemo-EIA, sensitivity 54.4%). The accuracy of OC Light was similar to that of Feca-EIA, with sensitivity ranging from 38.9% (specificity 96.8%) to 68.9% (specificity 94.6%) and specificity ranging from 93.9% (sensitivity 63.7%) to 98.3% (sensitivity 41.1%).

One study evaluated both Feca-EIA and OC Light,[88] and another evaluated Iatro Hemcheck and OC Light,[89] for the detection of all neoplasms. Both studies reported that OC Light was more sensitive (68.9% vs 46.2%[88] and 63.7% vs 56.8%[89]), with specificities being similar. One study evaluated four immunochemical FOBTs, Feca-EIA, Immudia HemSp, LA Hemochaser and OC Light.[2] Of these LA Hemochaser was the most sensitivie (76.7%), followed by Feca-EIA (65.6%), Immudia HemSp (54.7%) and OC Light (38.9%). Specificity was highest for OC Light (96.8%), followed by LA Hemochaser (94.7%), Feca-EIA (81.9%) and Immudia HemSp (77.0%). A study that evaluated three EIA-FOBTs (Feca-EIA, Hemo-EIA and Stick-EIA), also evaluated Immudia HemSp, MonoHaem and OC Light.[1] The FOBT with the highest sensitivity was Stick-EIA (72.2%), followed by Hemo-EIA (54.4%), Immudia-HemSp (43.3%), OC Light (41.1%), Feca-EIA (32.2%) and MonoHaem (25.6%).

Three FOBTs, Hemo-EIA, MonoHaem and OC Light, had the same specificity (98.3%) followed by Stick-EIA (91.9%), Feca-EIA (91.4%) and Immudia HemSp (79.2%). The main results are presented in figures 18 and 19, and all results are presented in table 2.

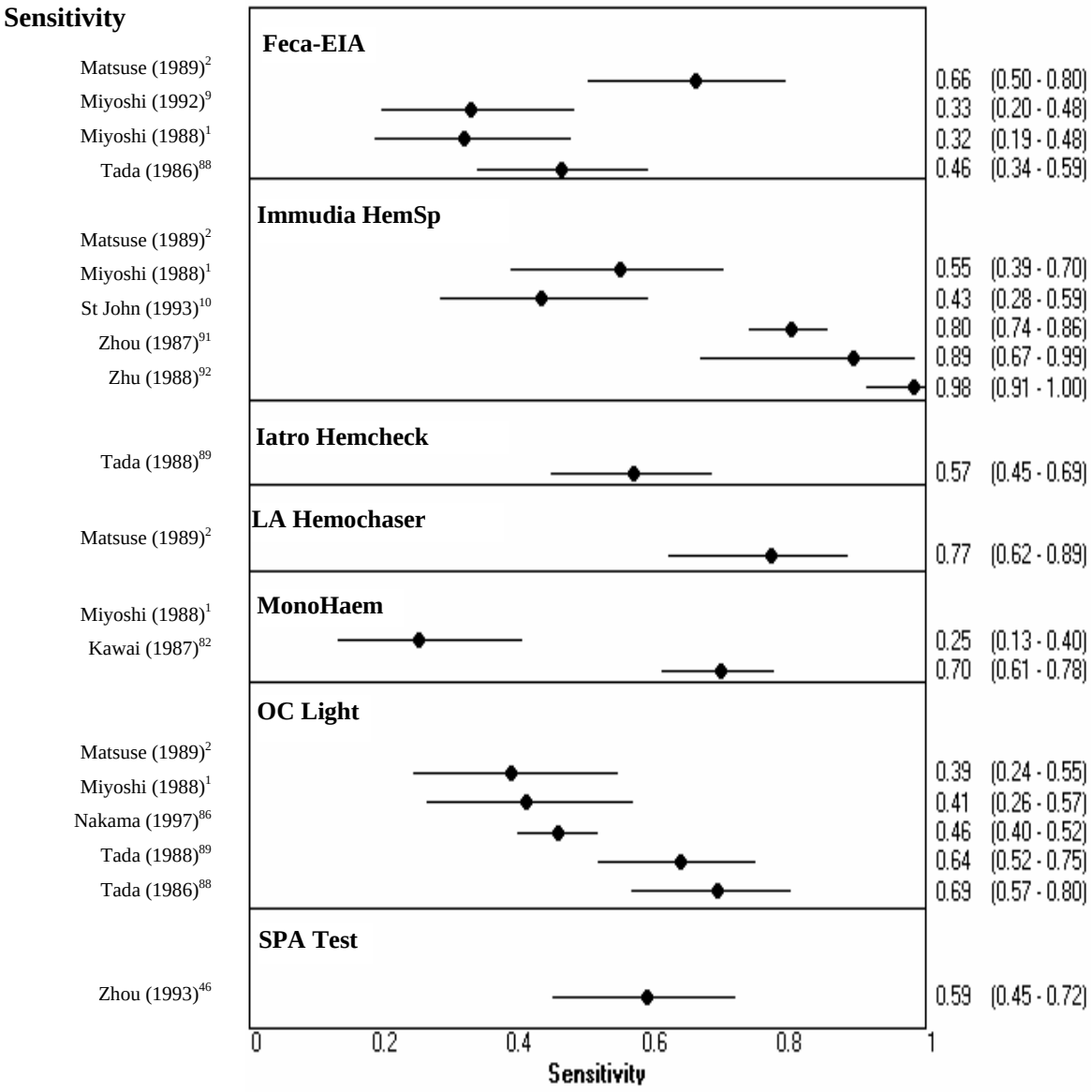


Figure 18a: The sensitivity of immunochemical FOBTs for the detection of all neoplasms as reported in diagnostic case-control studies

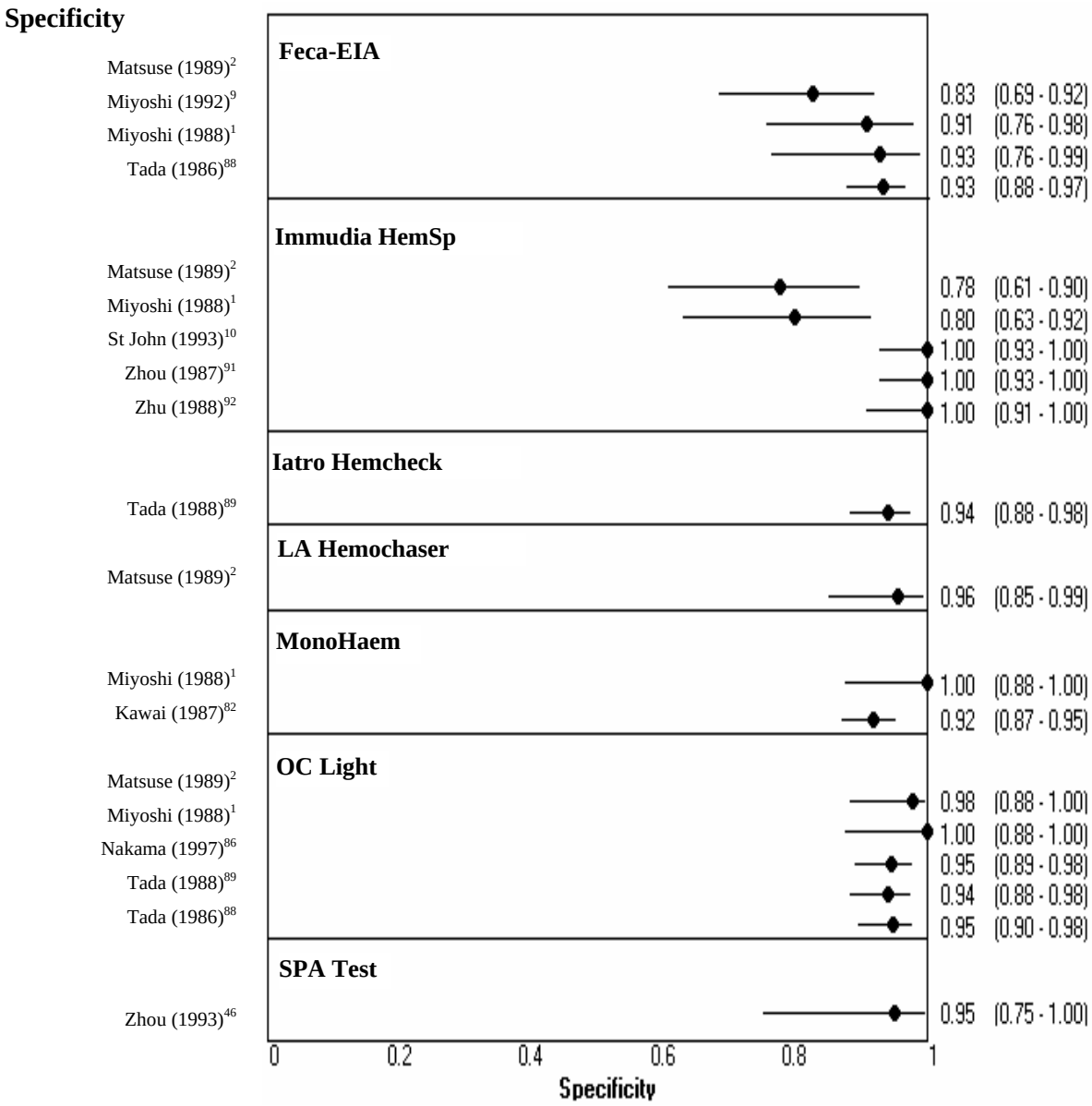


Figure 18b: The specificity of immunochemical FOBTs for the detection of all neoplasms as reported in diagnostic case-control studies

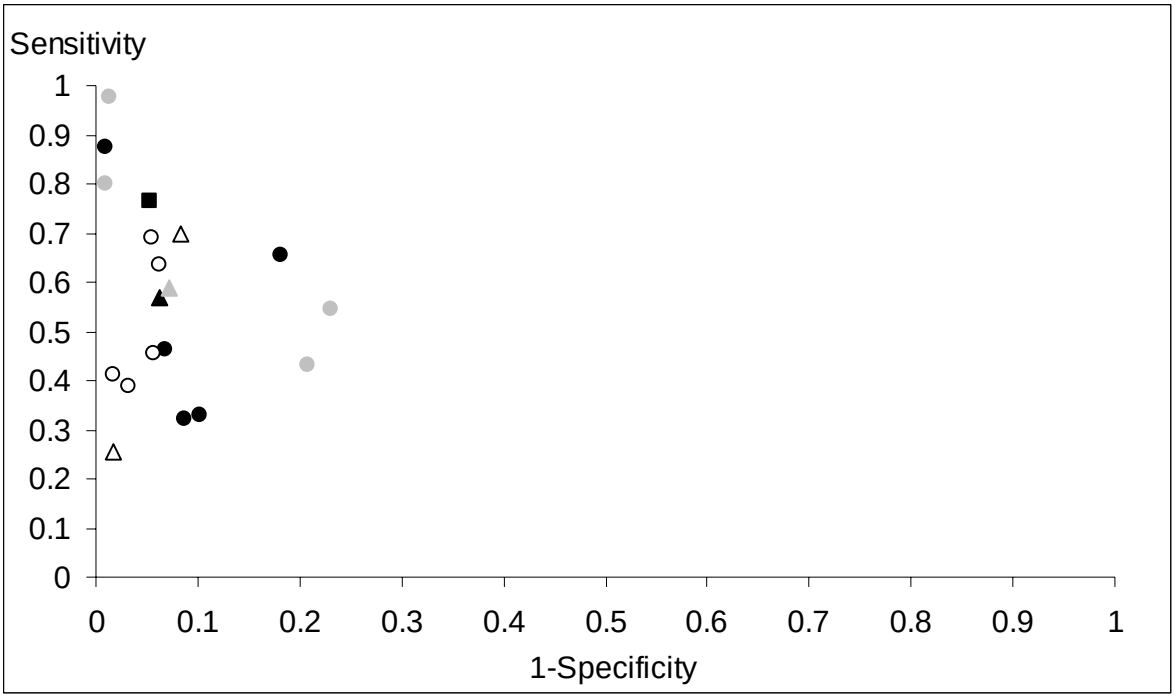


Figure 19: The detection of all neoplasms using Feca-EIA (●), OC Light (◯), Immudia HemSp (◍), Iatro Hemcheck (▲), LA Hemochaser (■), MonoHaem (△), and the SPA test (◬), based on the results of the diagnostic case-control studies

4.3.3 Diagnosis of colorectal cancer using immunochemical FOBTs

Fifteen diagnostic cohorts evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of CRC. Two evaluated Flexsure,[5, 108] four Immudia HemSp,[8, 73, 95, 103] one Iatro Hemcheck,[74] three MonoHaem,[75, 76, 102] four OC Light[71, 96, 98, 99] and one SPA test.[46] The reference standards used for people with a positive FOBT included colonoscopy,[5, 71, 73-76, 96, 98, 103, 108] colonoscopy, with barium enema in 2% of people,[102] colonoscopy and follow-up,[8] or sigmoidoscopy,[46, 95, 99] The reference standards used for people with a negative FOBT included colonoscopy,[71, 73-76, 96, 103] flexible colonoscopy,[5] sigmoidoscopy,[46, 99, 108] registry and follow-up,[8, 102] follow-up,[95] or health insurance claims.[98] Eight studies recruited an appropriate patient spectrum.[8, 71, 73, 74, 95, 96, 98, 108] There was statistically significant between study heterogeneity (Cochrane Q<0.05 and/or I^2>75%) in all test groups, therefore pooling was not undertaken.

Overall, the sensitivity for the detection of CRC ranged from 1.7% (Flexsure, specificity 94.6%) to 98.0% (MonoHaem, specificity 95.6%), and specificity from 88.8% (SPA Test, sensitivity 50.0%) to 99.9% (MonoHaem, sensitivity 6.7%). Iatro HemCheck seemed to be one of the most accurate immunochemical FOBTs, but was evaluated in only one study that reported a sensitivity of 82.0% and specificity of 95.7%.[74] The sensitivities of both Flexsure and OC Light varied widely, ranging from 1.7% to 79.2% and 23.7% to 86.1%, respectively. Although the highest sensitivities reported for Immudia HemSp were generally lower than those for other tests, the results were more consistent, with the range of sensitivities being narrower, between 42.1% and 68.2%. The reported specificities of all the FOBTs in this section were similar. One study compared the accuracy of OC light and Feca-EIA when one, two and three stools were tested.[6] This study reported an increase in sensitivity with the number of stools tested for both FOBTs. Sensitivity ranged from 85.5% (specificity 88.7%) for OC Light and 66.7% (specificity 86.7%) for Feca-EIA when one stool was tested, to 93.3% (specificity 83.3%) for OC Light and 82.3% (specificity 79.0%) for Feca-EIA when three were tested.[6] The main results are presented in figures 20 and 21, and all results are presented in table 2.

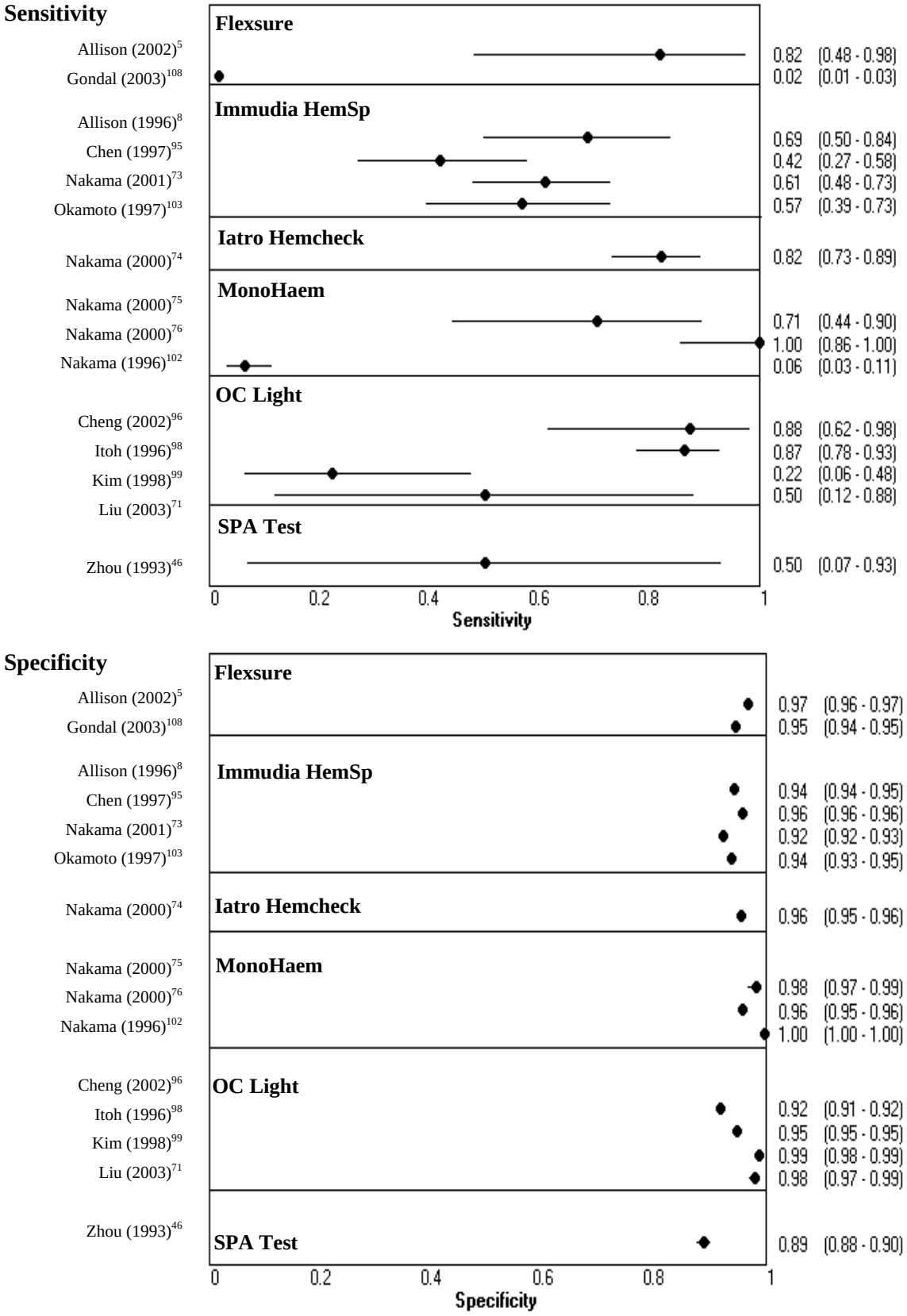


Figure 20: The sensitivity and specificity of immunochemical FOBTs for the detection of CRC as reported in diagnostic cohort studies

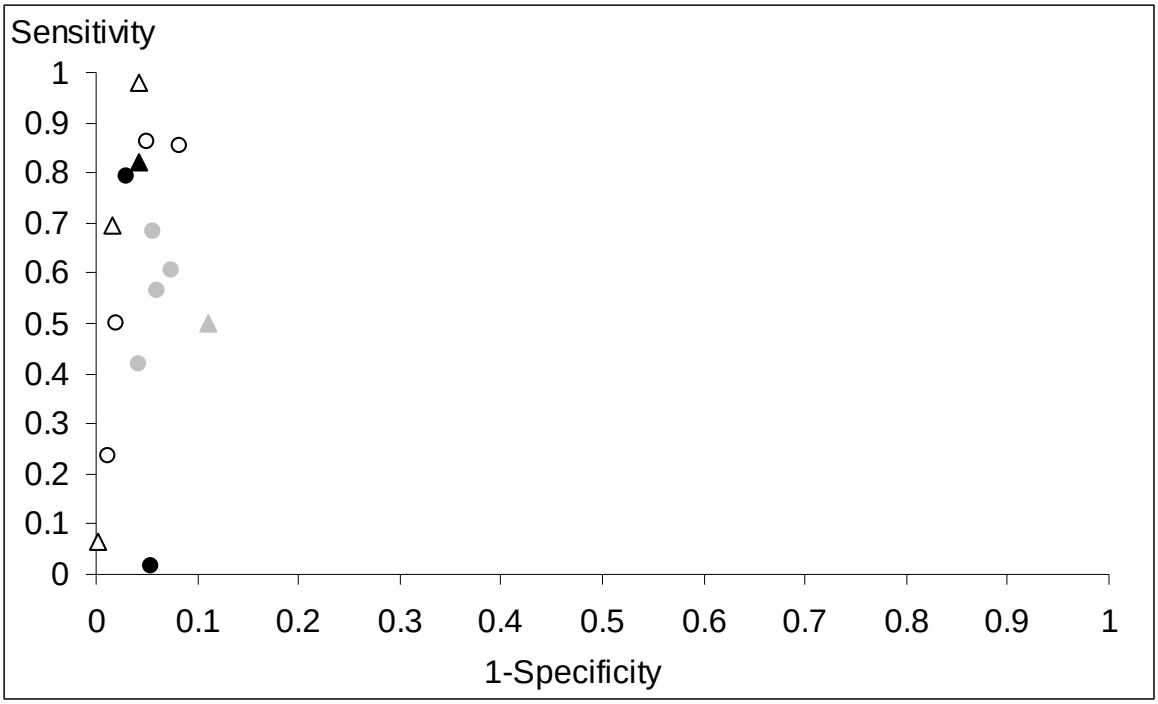
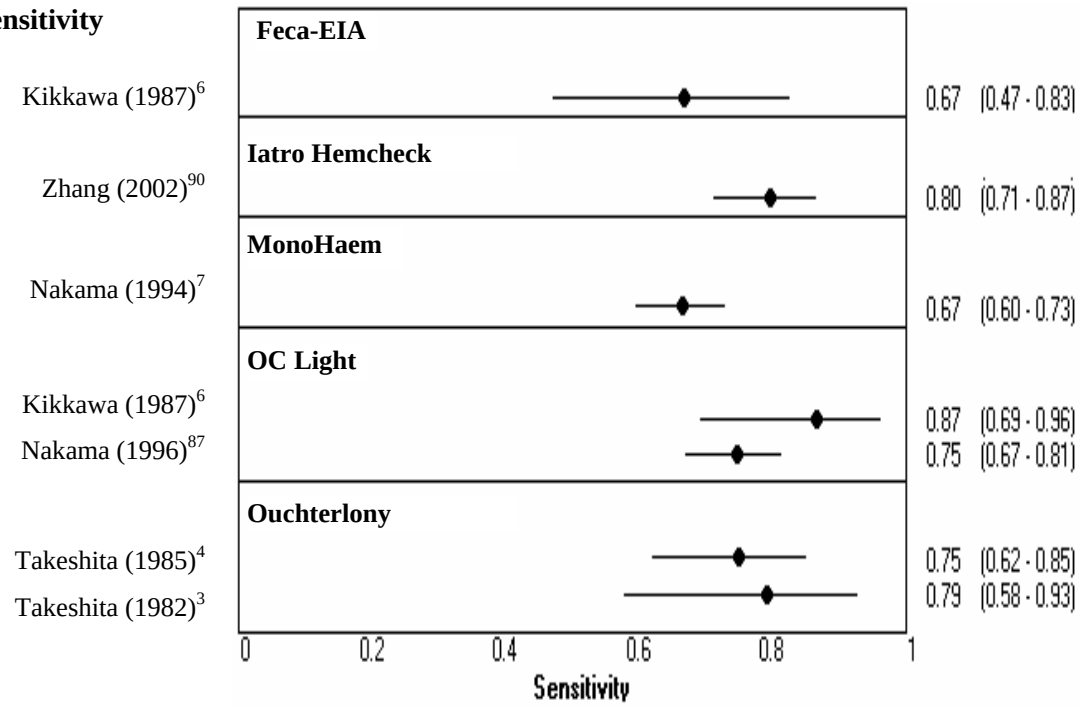


Figure 21: The detection of colorectal cancers using Flexsure (●), OC Light (○), Immudia HemSp (◍), Iatro Hemcheck (▲), MonoHaem (△), and the SPA test (◬), based on the results of the diagnostic cohort studies

Six diagnostic case-control studies evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of CRC. One evaluated Feca-EIA,[6] one Iatro Hemcheck,[90] one MonoHaem,[7] two OC Light[6, 87] and two Ouchterlony.[3, 4] The reference standards used to diagnose disease in cases included colonoscopy[87, 90], or colonoscopy and barium enema.[7] The reference standard used to verify the disease-free status of controls was upper and lower tract endoscopy.[7, 87, 90] The reference standard was not reported for either cases or controls in three studies.[3, 4, 6]

Studies generally reported higher sensitivity and specificity values, for the detection of CRC, than those derived from diagnostic cohort studies. OC Light had sensitivities of 85.5% (specificity 88.7%) and 74.5% (specificity 91.9%), Iatro HemCheck 79.6% (specificity 96.3%), Ouchterlony 78.0% (specificity 97.6%) and 74.6% (specificity 98.4%), Feca-EIA 66.7% (specificity 86.7%), and MonoHaem, with the lowest reported sensitivity, 66.4% (specificity 95.5%). The main results are presented in figures 22 and 23, and all results are presented in table 2.

Sensitivity



Specificity

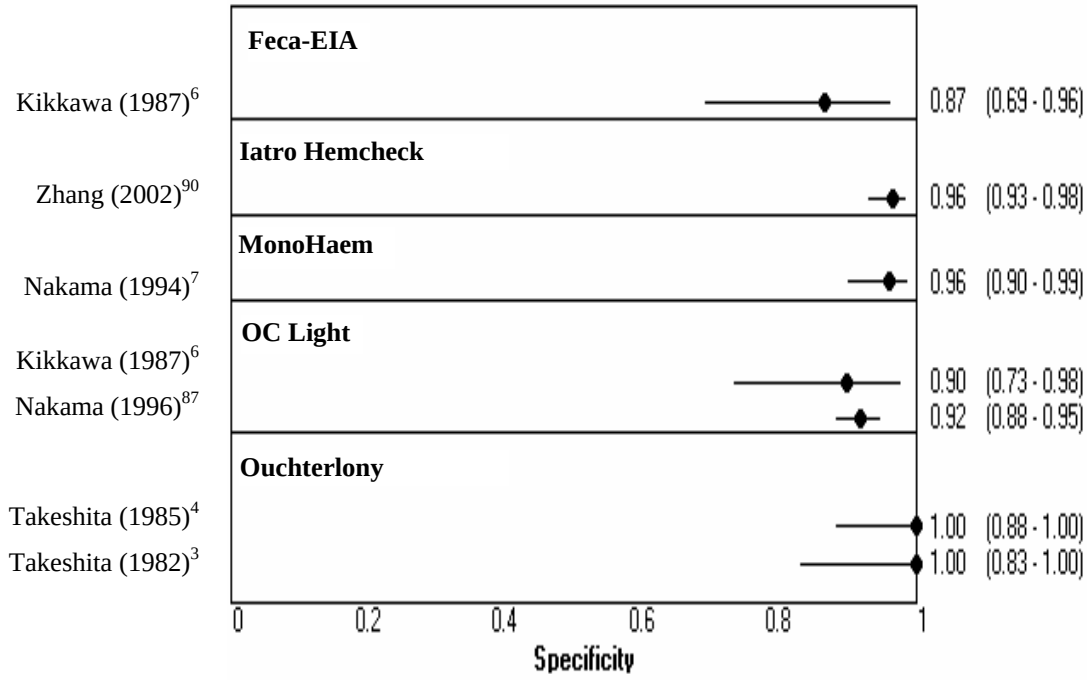


Figure 22: The sensitivity and specificity of immunochemical FOBTs for the detection of CRC as reported in diagnostic case-control studies

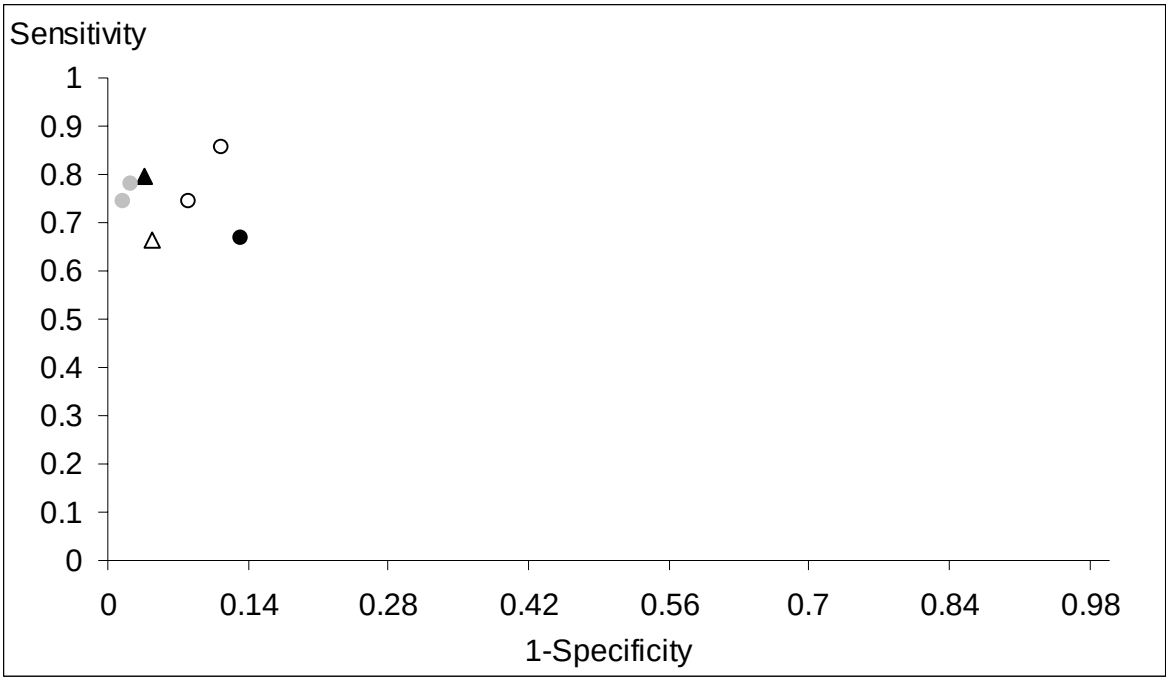


Figure 23: The detection of colorectal cancers using Feca-EIA (●), OC Light (○), Iatro Hemcheck (▲), MonoHaem (△), and Ouchterlony (◍), based on the results of the diagnostic case-control studies

4.3.4 Diagnosis of all adenomas using immunochemical FOBTs

Five diagnostic cohorts evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of all adenomas. One evaluated Flexsure,[108] one Immudia HemSp,[73] two OC Light[71, 96] and one SPA test.[46] Three studies used colonoscopy after both a positive and negative FOBT result, [71, 73, 96] one used colonoscopy after a positive FOBT and sigmoidoscopy after a negative result,[108] and the fifth used sigmoidoscopy after both positive and negative results.[46] Only one study did not recruit an appropriate patient spectrum.[46]

The accuracy of immunochemical tests for the detection of adenomas varied greatly, with the sensitivities ranging from 4.4% (OC Light, specificity 98.5%) to 63.0% (Immudia HemSp, specificity 94.3%), although specificity was similar for all tests, ranging from 89.4% (SPA Test, sensitivity 28.5%) to 98.5% (OC Light, sensitivity 4.4%). Immudia HemSp was the only FOBT reported to have reasonable accuracy in the detection of adenomas, although this test was evaluated in only one study.[73] The main results are presented in figures 24 and 25, and all results are presented in table 2.

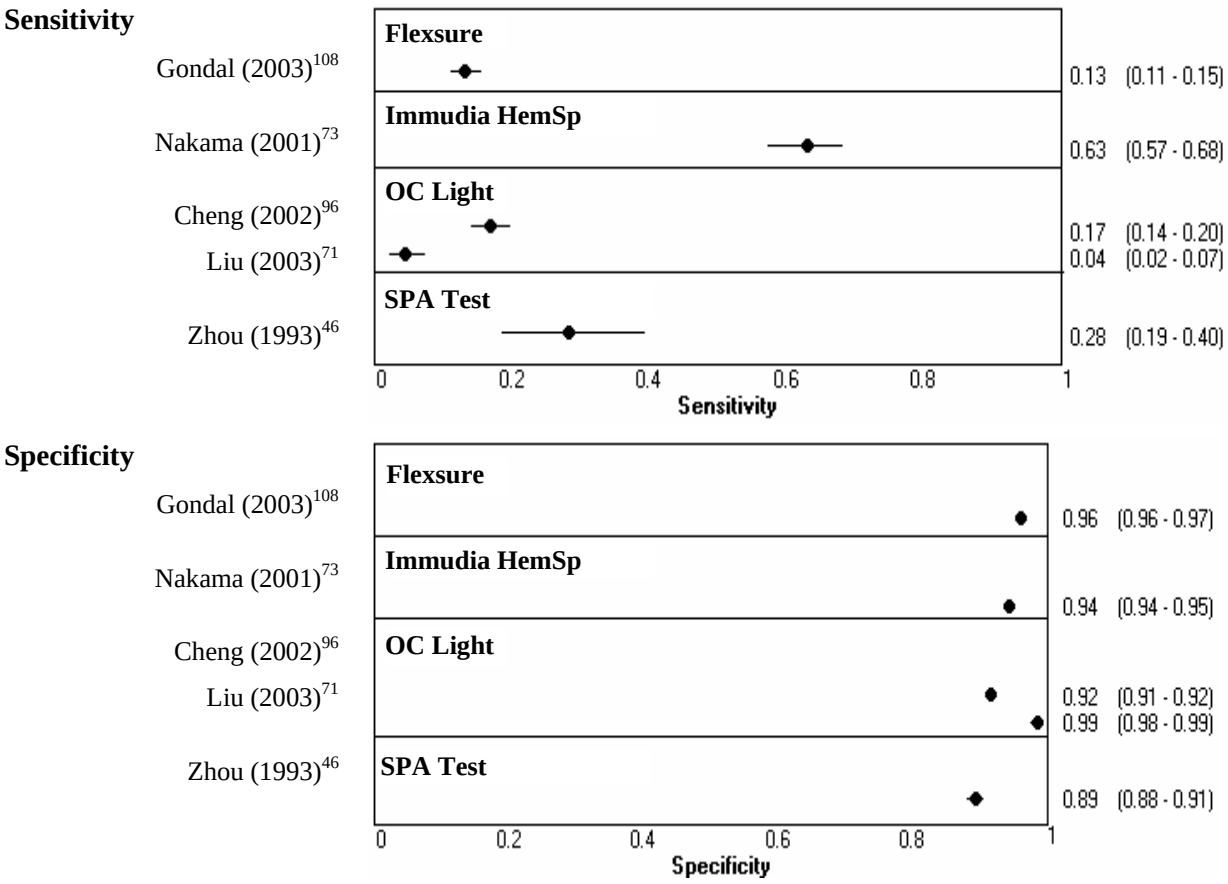


Figure 24: The sensitivity and specificity of immunochemical FOBTs for the detection of all adenomas as reported in diagnostic cohort studies

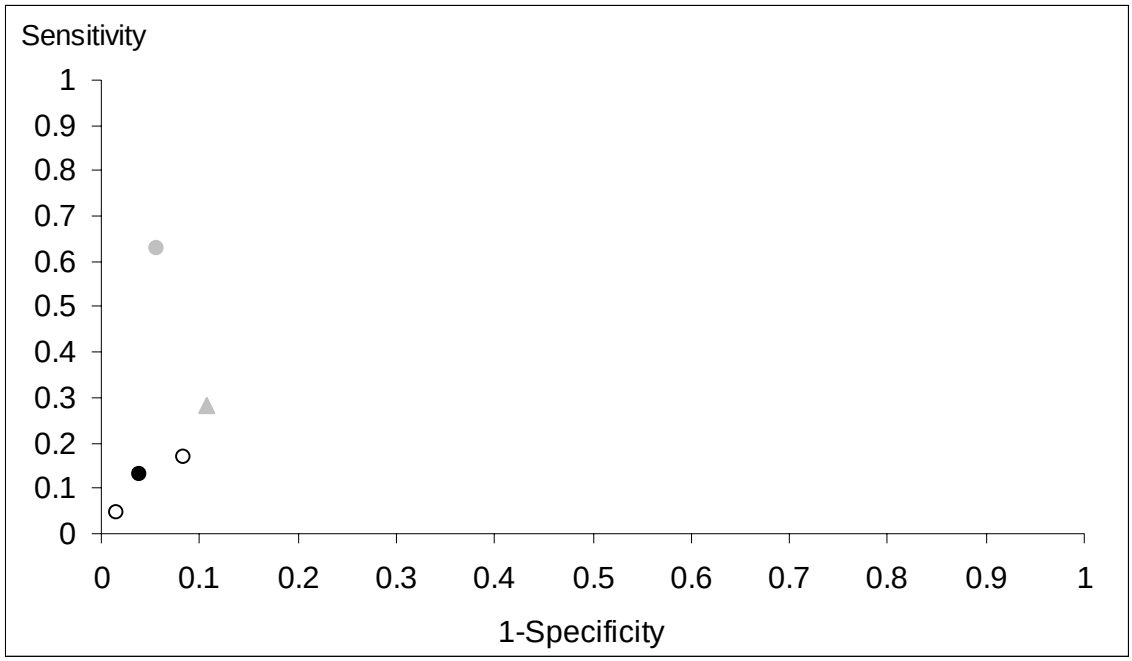


Figure 25: The detection of all adenomas using Flexsure (●), Immudia HemSp (◍), OC Light (○) and the SPA test (△) based on the results of the diagnostic cohort studies

One diagnostic case-control study evaluated the diagnostic accuracy of OC Light to detect all adenomas.[85] This study used colonoscopy to verify disease in the cases and upper and lower tract endoscopy to verify the disease-free status of controls. The reported sensitivity was high, 91.0%, and specificity was 42.8%. The results are presented in table 2.

4.3.5 Diagnosis of adenomas 1cm or larger using immunochemical FOBTs

Four diagnostic cohorts evaluated the diagnostic accuracy of immunochemical FOBTs for the detection of adenomas of 1cm or larger. Two evaluated Flexsure[5, 108] and two evaluated Immudia HemSp.[8, 73] The reference standard used in all studies for people with a positive FOBT was colonoscopy.[5, 8, 73, 108] The reference standards used for people with a negative FOBT included colonoscopy,[5, 73] sigmoidoscopy,[108] or referral to the registry and follow-up.[8] Only one study did not recruit an appropriate patient spectrum.[5]

Both studies evaluating Immudia HemSp reported substantially higher sensitivities (66.5% and 58.5%) than the studies evaluating Flexsure (29.6% and 27.7%). The specificities were similar in all studies, ranging from 93.1% to 97.3%. The main results are presented in figures 26 and 27, and all results are presented in table 2.

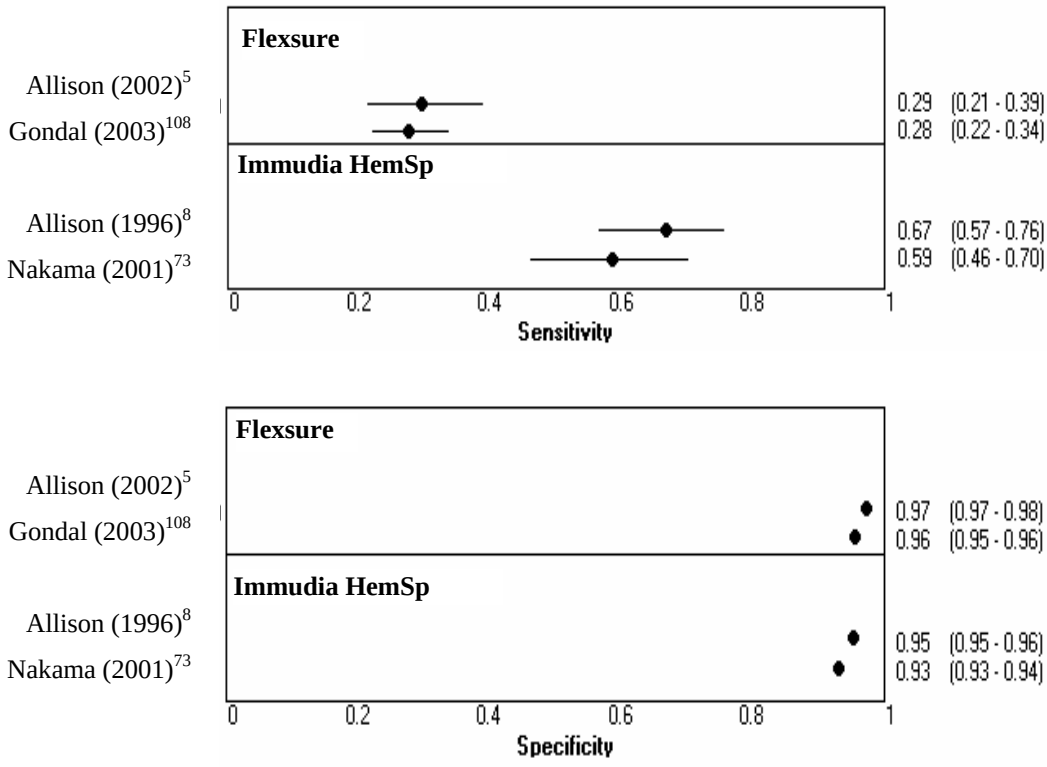


Figure 26: The sensitivity and specificity of immunochemical FOBTs for the detection of adenomas >1cm as reported in diagnostic cohort studies

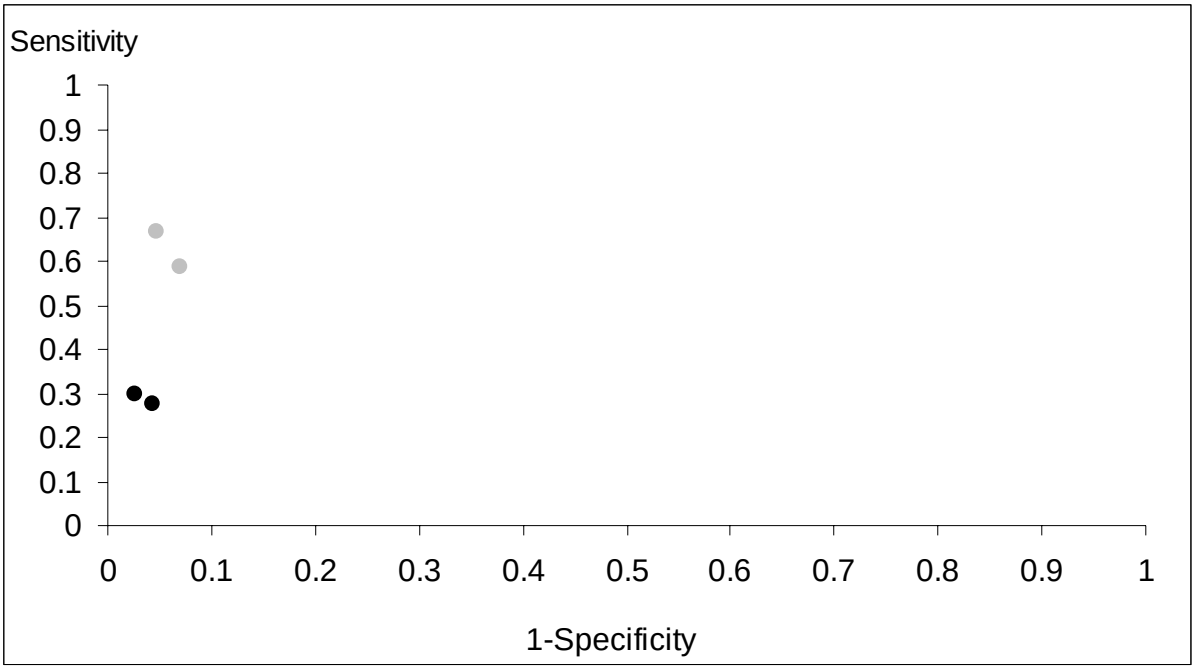
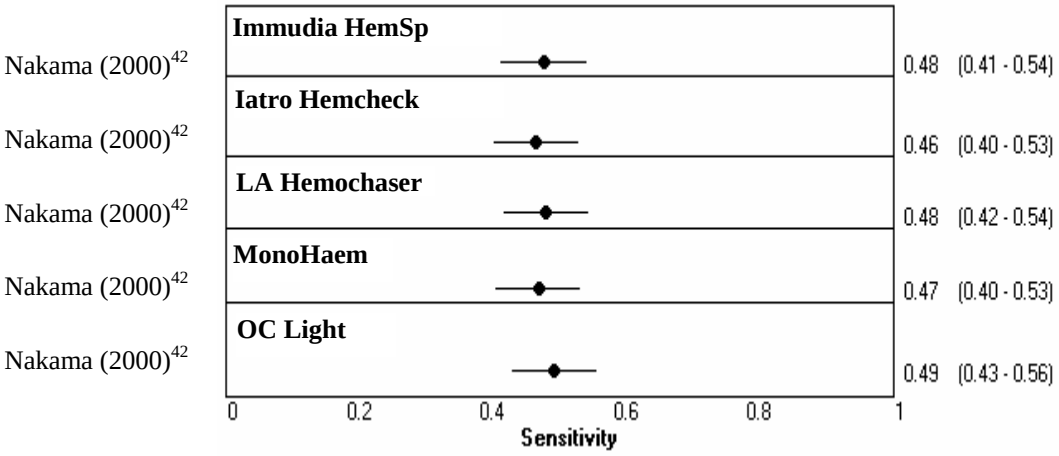


Figure 27: The detection of adenomas of 1cm or larger using Flexsure (●) and Immudia HemSp (●) based on the results for the diagnostic cohort studies

One diagnostic case-control study evaluated the diagnostic accuracy of Immudia HemSp, Iatro Hemcheck, LA Hemochaser, MonoHaem, and OC Light for the detection of adenomas of 1cm or larger.[42]This study used colonoscopy to verify disease in the cases and upper and lower tract endoscopy to verify the disease-free status of controls. Sensitivity and specificity were similar for all tests studied, with sensitivity ranging from 46.4% (Iatro Hemcheck, specificity 95.0%) to 49.2% (OC Light, specificity 95.4%) and specificity from 95.0% (Iatro Hemcheck, sensitivity 46.4%) to 96.6% (Immudia HemSp, sensitivity 47.6%). The main results are presented in figures 28 and 29, and all results are presented in table 2.

Sensitivity



Specificity

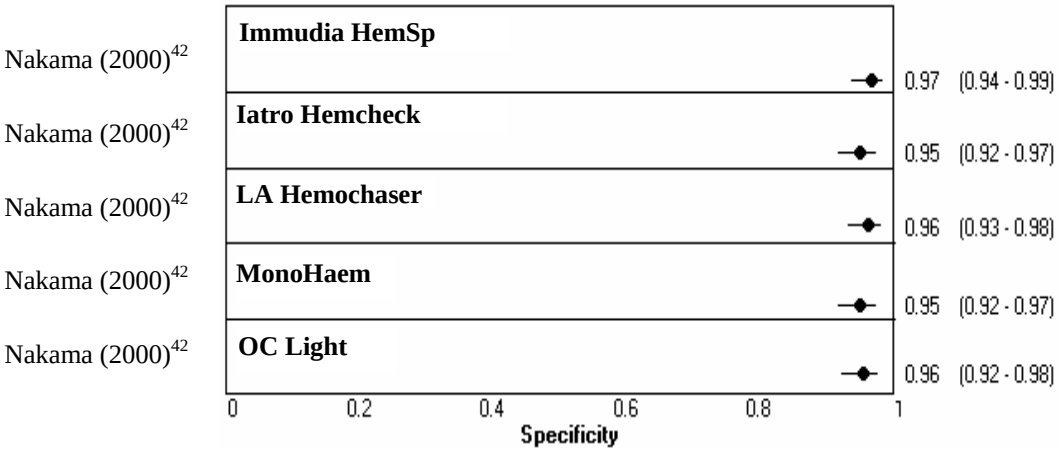


Figure 28: The sensitivity and specificity of immunochemical FOBTs for the detection of adenomas of 1cm or larger as reported in the diagnostic case-control study

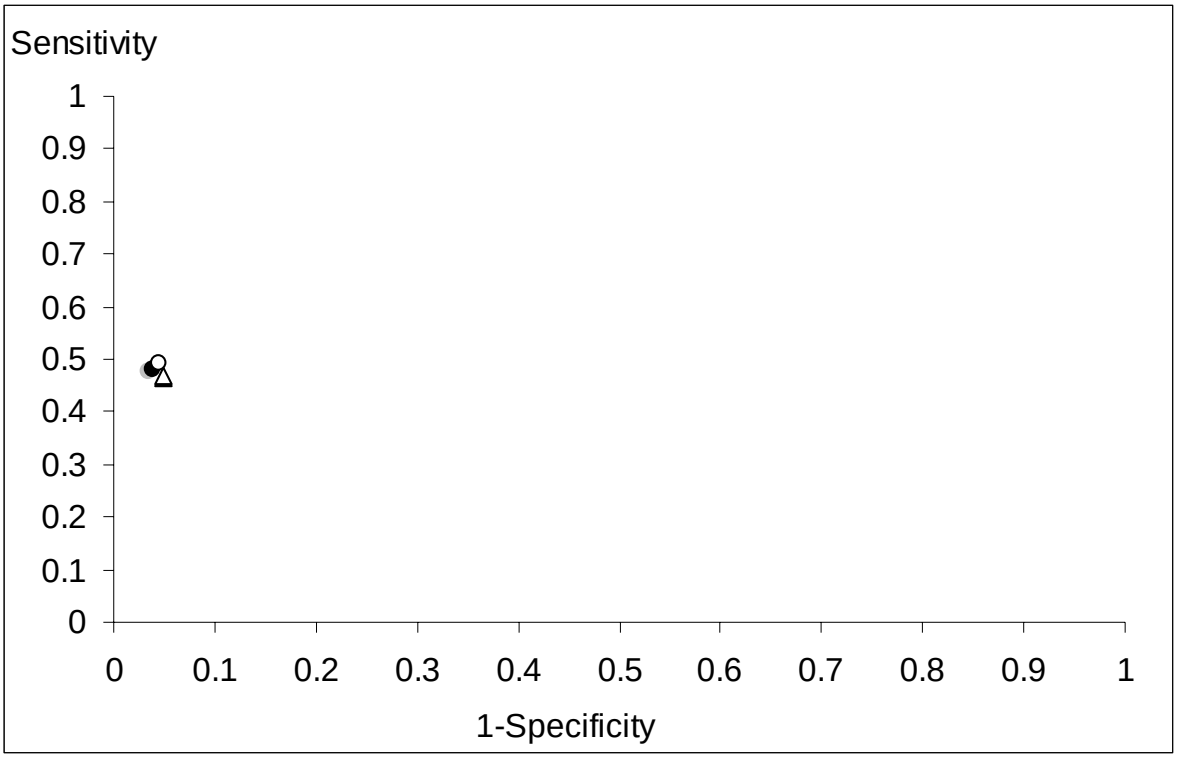


Figure 29: The detection of adenomas of 1cm or larger using Immudia HemSp (◯), Iatro Hemcheck (▲), LA Hemochaser (●), MonoHaem (△), and OC Light (◯) based on the results of one diagnostic case-control study

Table 2: Results of studies that evaluated immunochemical FOBTs

Study ID	Index test	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
All neoplasms													
Matsuse (1989)[2]	Feca-EIA	Case-control	C/BE	C and/or BE	29	8	15	38	65.6 (49.9, 79.1)	81.9 (68.0, 91.6)	3.62 (1.90, 6.90)	0.42 (0.28, 0.64)	8.62 (3.29, 22.61)
Miyoshi (1992)[9]	Feca-EIA	Case-control	C	C and/or BE	15	3	31	30	33.0 (20.0, 48.2)	89.7 (74.4, 97.5)	3.20 (1.10, 9.37)	0.75 (0.59, 0.94)	4.29 (1.21, 15.15)
Miyoshi (1988)[1]	Feca-EIA	Case-control	NR	NR	14	2	30	26	32.2 (19.1, 47.8)	91.4 (74.9, 98.5)	3.74 (1.06, 13.16)	0.74 (0.59, 0.93)	5.04 (1.19, 21.26)
Miyoshi (1988)[1]	Hemo-EIA	Case-control	NR	NR	24	0	20	28	54.4 (38.9, 69.4)	98.3 (85.0, 100)	31.58 (2.00, 499.32)	0.46 (0.34, 0.64)	68.12 (3.91, 1185.80)
Miyoshi (1988)[1]	Stick-EIA	Case-control	NR	NR	32	2	12	28	72.2 (56.9, 84.5)	91.9 (76.4, 98.6)	8.96 (2.69, 29.80)	0.30 (0.19, 0.49)	29.64 (6.97, 126.11)
Tada (1986)[88]	Feca-EIA	Case-control	C/BE	C and/or BE	30	9	35	128	46.2 (33.9, 58.9)	93.1 (87.5, 96.7)	6.71 (3.45, 13.07)	0.58 (0.46, 0.73)	11.62 (5.13, 26.32)
Allison (2002)[5]	FlexSure	Cohort	C	C	40	133	81	5102	33.2 (24.9, 42.3)	97.5 (97.0, 97.9)	13.02 (9.62, 17.62)	0.69 (0.61, 0.78)	18.99 (12.55, 28.74)
Gondal (2003)[108]	FlexSure	Cohort	C	S	133	169	799	4344	14.3 (12.1, 16.7)	96.2 (95.6, 96.8)	3.81 (3.07, 4.73)	0.89 (0.87, 0.92)	4.28 (3.37, 5.44)
Matsuse (1989)[2]	Immudia HemSp	Case-control	C/BE	C and/or BE	23	8	19	28	54.7 (38.8, 69.9)	77.0 (6.0, 89.2)	2.38 (1.24, 4.56)	0.59 (0.41, 0.85)	4.04 (1.53, 10.69)
Miyoshi (1988)[1]	Immudia HemSp	Case-control	NR	NR	19	7	25	28	43.3 (28.6, 58.9)	79.2 (62.4, 90.9)	2.08 (1.01, 4.27)	0.72 (0.53, 0.97)	2.91 (1.07, 7.88)
St John (1993)[10]	Immudia HemSp	Case-control	C	NR	151	0	37	50	80.2 (73.8, 85.6)	99.0 (91.2, 100)	81.76 (5.18, 1290.70)	0.20 (0.15, 0.27)	408.04 (24.61, 6766.30)
Zhou (1987)[91]	Immudia HemSp	Case-control	NR	NR	17	0	2	50	87.5 (65.1, 97.9)	99.0 (91.2, 100)	89.25 (5.63, 1414.6)	0.13 (0.04, 0.40)	707.00 (32.24, 15455.1)
Zhu (1988)[92]	Immudia HemSp	Case-control	NR	NR	62	0	1	39	97.7 (90.4, 99.8)	98.8 (88.9, 100)	78.13 (4.97, 1227.80)	0.02 (0.01, 0.12)	3291.67 (130.82, 82823.40)
Nakama (2001)[73]	Immudia HemSp	Cohort	C	C	240	546	143	9023	62.6 (57.6, 67.5)	94.3 (93.8, 94.7)	10.97 (9.80, 12.27)	0.40 (0.35, 0.45)	27.67 (22.12, 34.62)
Tada (1988)[89]	Iatro HemCheck	Case-control	NR	NR	41	7	31	114	56.8 (44.7, 68.4)	93.9 (88.0, 97.4)	9.25 (4.49, 19.03)	0.46 (0.35, 0.60)	20.11 (8.41, 48.10)
Matsuse (1989)[2]	LA Hemochaser	Case-control	C/BE	C and/or BE	34	2	10	44	76.7 (61.7, 88.0)	94.7 (83.9, 99.1)	14.41 (4.27, 48.67)	0.25 (0.14, 0.42)	58.49 (13.73, 249.13)
Miyoshi (1988)[1]	MonoHaem	Case-control	NR	NR	11	0	33	28	25.6 (13.7, 40.7)	98.3 (85.0, 100)	14.82 (0.91, 241.97)	0.76 (0.63, 0.91)	19.57 (1.10, 346.89)

Study ID	Index test	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Kawai (1987)[82]	MonoHaem	Case-control	C/BE	C and/or BE	88	16	38	181	69.7 (60.9, 77.5)	91.7 (86.9, 95.1)	8.36 (5.20, 13.46)	0.33 (0.25, 0.43)	25.29 (13.46, 47.49)
Liu (2003)[71]	OC Light	Cohort	C	C	15	16	272	1084	5.4 (3.1, 8.7)	98.5 (97.6, 99.1)	3.59 (1.82, 7.10)	0.96 (0.93, 0.99)	3.74 (1.85, 7.57)
Cheng (2002)[96]	OC Light	Cohort	C	C	132	562	587	6130	18.4 (15.6, 21.4)	91.6 (90.9, 92.2)	2.19 (1.84, 2.60)	0.89 (0.86, 0.92)	2.46 (2.00, 3.02)
Matsuse (1989)[2]	OC Light	Case-control	C/BE	C and/or BE	17	1	27	45	38.9 (24.7, 54.6)	96.8 (87.0, 99.8)	12.19 (2.42, 61.36)	0.63 (0.50, 0.80)	19.30 (3.41, 109.25)
Miyoshi (1988)[1]	OC Light	Case-control	NR	NR	18	0	26	28	41.1 (26.7, 56.8)	98.3 (85.0, 100)	23.84 (1.49, 380.52)	0.60 (0.47, 0.77)	39.79 (2.28, 693.72)
Nakama (1997)[86]	OC Light	Case-control	C	C	126	7	150	123	45.7 (39.7, 51.7)	94.3 (88.8, 97.6)	7.98 (3.94, 16.17)	0.58 (0.51, 0.65)	13.84 (6.38, 30.02)
Tada (1988)[89]	OC Light	Case-control	NR	NR	46	7	26	114	63.7 (51.6, 74.6)	93.9 (88.0, 97.4)	10.36 (5.07, 21.17)	0.39 (0.28, 0.53)	26.79 (11.12, 64.55)
Tada (1986)[88]	OC Light	Case-control	C/BE	C and/or BE	45	7	20	130	68.9 (56.4, 79.8)	94.6 (89.4, 97.7)	12.68 (6.21, 25.92)	0.33 (0.23, 0.47)	38.62 (15.67, 95.17)
Zhou (1993)[46]	SPA Test	Cohort	S	S	24	274	56	2304	30.2 (20.5, 41.5)	89.4 (88.1, 90.5)	2.84 (2.00, 4.03)	0.78 (0.68, 0.90)	3.64 (2.23, 5.94)
Zhou (1993)[46]	SPA Test	Case-control	S	S	33	1	23	19	58.8 (45.0, 71.6)	92.9 (72.8, 99.5)	8.23 (1.73, 39.05)	0.44 (0.32, 0.62)	18.53 (3.25, 105.84)
Chen (2002)[66]	Unspecified	Cohort	C	C	26	745	33	1383	44.1 (31.2, 57.6)	65.0 (62.9, 67.0)	1.26 (0.94, 1.69)	0.86 (0.69, 1.08)	1.46 (0.87, 2.46)
Morikawa (2004)[101]	Unspecified	Cohort	C	C	456	845	3989	17453	10.3 (9.4, 11.2)	95.4 (95.1, 95.7)	2.22 (1.99, 2.48)	0.94 (0.93, 0.95)	2.36 (2.10, 2.66)
CRC													
Kikkawa (1987)[6]	Feca-EIA-1 day	Case-control	NR	NR	20	4	10	26	66.7 (47.2, 82.7)	86.7 (69.3, 96.2)	5.00 (1.94, 12.887)	0.39 (0.23, 0.65)	13.00 (3.55, 47.60)
	Feca-EIA-2 days				24	6	6	24	80.0 (61.4, 92.3)	80.0 (61.4, 92.3)	4.00 (1.91, 8.37)	0.25 (0.12, 0.52)	16.00 (4.52, 56.70)
	Feca-EIA-3 days				25	6	5	24	82.3 (64.4, 93.6)	79.0 (60.7, 91.5)	3.92 (1.94, 7.92)	0.22 (0.10, 0.49)	17.48 (4.94, 61.84)
Allison (2002)[5]	FlexSure	Cohort	C	C	9	164	2	5181	79.2 (47.1, 96.4)	96.9 (96.4, 97.4)	25.73 (18.55, 35.68)	0.21 (0.07, 0.65)	119.69 (29.46, 486.26)
Gondal (2003)[108]	FlexSure	Cohort	C	S	13	289	795	5039	1.7 (0.9, 2.8)	94.6 (93.9, 95.2)	0.31 (0.18, 0.53)	1.04 (1.03, 1.05)	0.30 (0.17, 0.51)
Allison (1996)[8]	Immudia HemSp	Cohort	C/FU	CR/FU	22	418	10	7043	68.2 (49.7, 83.2)	94.4 (93.8, 94.9)	12.16 (9.46, 15.63)	0.34 (0.21, 0.56)	36.07 (17.22, 75.52)
Chen (1997)[95]	Immudia HemSp	Cohort	S	FU	18	2628	25	59940	42.0 (27.3, 57.9)	95.8 (95.9, 95.6)	10.01 (7.06, 14.19)	0.60 (0.47, 0.78)	16.54 (9.08, 30.14)
Nakama (2001)[73]	Immudia HemSp	Cohort	C	C	39	747	25	9141	60.8 (47.9, 72.7)	92.4 (91.9, 93.0)	8.04 (6.54, 9.89)	0.42 (0.31, 0.57)	18.94 (11.45, 31.34)

Study ID	Index test	Study design	Reference standard* +ve/ case	Reference standard* -ve/ control	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Okamoto (1997)[103]	Immudia HemSp	Cohort	C	C	21	338	16	5273	56.6 (39.6, 72.5)	94.0 (93.3, 94.6)	9.38 (6.97, 12.63)	0.46 (0.32, 0.66)	20.30 (10.59, 38.92)
Zhang (2002)[90]	Iatro HemCheck	Case-control	C	ULTE	91	8	23	220	79.6 (71.0, 86.5)	96.3 (93.0, 98.3)	21.44 (11.01, 41.73)	0.21 (0.15, 0.31)	101.01 (44.42, 229.67)
Nakama (2000)[74]	Iatro HemCheck	Cohort	C	C	79	753	17	16815	82.0 (72.8, 89.0)	95.7 (95.4, 96.0)	19.11 (17.01, 21.47)	0.19 (0.12, 0.29)	101.38 (60.11, 170.98)
Nakama (2000)[75]	MonoHaem	Cohort	C	C	12	8	5	497	69.4 (43.7, 88.5)	98.3 (96.8, 99.2)	41.34 (19.85, 86.10)	0.31 (0.16, 0.62)	133.02 (39.65, 446.33)
Nakama (2000)[76]	MonoHaem	Cohort	C	C	24	360	0	8351	98.0 (82.8, 100)	95.9 (95.4, 96.3)	23.68 (21.10, 26.58)	0.02 (0, 0.32)	1135.16 (68.90, 18703.5)
Nakama (1996)[102]	MonoHaem	Cohort	C (BE in 2%)	CR/FU	10	4	147	3204	6.6 (3.3, 11.7)	99.9 (99.7, 100)	47.39 (15.89, 141.33)	0.93 (0.90, 0.98)	50.69 (16.60, 154.84)
Nakama (1994)[7]	MonoHaem	Case-control	C/BE	ULTE	133	4	67	96	66.4 (59.4, 72.9)	95.5 (89.5, 98.6)	14.91 (6.01, 36.98)	0.35 (0.29, 0.43)	42.41 (15.77, 114.09)
Cheng (2002)[96]	OC Light	Cohort	C	C	14	600	2	6715	85.3 (60.0, 97.5)	91.8 (91.1, 92.4)	10.39 (8.41, 12.84)	0.16 (0.05, 0.50)	64.86 (16.90, 248.90)
Itoh (1996)[98]	OC Light	Cohort	C	HIC	77	1413	12	26358	86.1 (77.2, 92.5)	94.9 (94.6, 95.2)	16.92 (15.35, 18.65)	0.15 (0.09, 0.25)	115.62 (63.46, 210.62)
Kim (1998)[99]	OC Light	Cohort	S	S	4	89	14	7144	23.7 (7.6, 48.4)	98.8 (98.5, 99.0)	19.14 (8.32, 44.03)	0.77 (0.60, 0.99)	24.77 (8.43, 72.80)
Liu (2003)[71]	OC Light	Cohort	C	C	3	28	3	1353	50.0 (13.9, 86.1)	97.9 (97.0, 98.6)	24.25 (10.62, 55.33)	0.51 (0.24, 1.07)	47.49 (10.31, 218.74)
Kikkawa (1987)[6]	OC Light-1 day	Case-control	NR	NR	26	3	4	27	85.5 (68.2, 95.5)	88.7 (72.2, 97.2)	7.57 (2.79, 20.53)	0.16 (0.07, 0.39)	46.27 (10.37, 206.39)
	OC Light-2 days				27	5	3	25	90.05 (73.5, 97.9)	83.3 (65.3, 94.4)	5.40 (2.41, 12.13)	0.12 (0.04, 0.36)	45.00 (9.73, 208.08)
	OC Light-3 days				28	5	2	25	93.3 (77.9, 99.2)	83.3 (65.3, 94.4)	5.60 (2.51, 12.54)	0.08 (0.02, 0.31)	70.00 (12.457, 393.36)
Nakama (1996)[87]	OC Light	Case-control	C	ULTE	112	24	38	276	74.5 (66.8, 81.2)	91.9 (88.2, 94.7)	9.15 (6.19, 13.53)	0.28 (0.21, 0.37)	32.98 (18.99, 57.27)
Takeshita (1985)[4]	Ouchterlony	Case-control	NR	NR	45	0	15	30	74.6 (61.8, 84.9)	98.4 (85.9, 100)	46.25 (2.95, 725.78)	0.26 (0.17, 0.40)	179.06 (10.32, 3105.8)
Takeshita (1982)[3]	Ouchterlony	Case-control	NR	NR	19	0	5	20	78.0 (57.1, 91.9)	97.6 (79.8, 100)	32.76 (2.10, 510.67)	0.23 (0.11, 0.47)	145.36 (7.53, 2807.2)
Zhou (1993)[46]	SPA Test	Cohort	S	S	2	296	2	2360	50.0 (9.4, 90.6)	88.8 (87.6, 90.0)	4.48 (1.85, 10.84)	0.56 (0.23, 1.35)	7.96 (1.37, 46.15)
Morikawa (2004)[101]	Unspecified	Cohort	C	C	48	1253	24	21418	66.7 (54.6, 77.3)	94.5 (94.2, 94.8)	12.06 (10.16, 14.33)	0.35 (0.26, 0.49)	34.19 (20.88, 55.99)

All adenomas													
Gondal (2003)[108]	FlexSure	Cohort	C	S	120	169	795	4244	13.2 (11.0, 15.5)	96.2 (95.6, 96.7)	3.43 (2.74, 4.28)	0.90 (0.88, 0.93)	3.79 (2.97, 4.85)
Nakama (2001)[73]	Immudia HemSp	Cohort	C	C	201	546	118	9023	63.0 (57.4, 68.3)	94.3 (93.8, 94.7)	11.03 (9.81, 12.40)	0.39 (0.34, 0.45)	28.08 (22.03, 35.79)
Cheng (2002)[96]	OC Light	Cohort	C	C	118	562	585	6128	16.8 (14.1, 19.8)	91.6 (90.9, 92.2)	2.00 (1.67, 2.40)	0.91 (0.88, 0.94)	2.21 (1.78, 2.74)
Liu (2003)[71]	OC Light	Cohort	C	C	12	16	269	1084	4.4 (2.3, 7.5)	98.5 (97.6, 99.1)	2.96 (1.44, 6.10)	0.97 (0.95, 1.00)	3.05 (1.44, 6.43)
Nakama (2004)[85]	OC Light	Case-control	C	ULTE	75	183	7	137	91.0 (82.6, 96.1)	42.8 (37.4, 48.8)	1.59 (1.42, 1.79)	0.21 (0.11, 0.42)	7.54 (3.45, 16.49)
Zhou (1993)[46]	SPA Test	Cohort	S	S	22	274	56	2304	28.5 (18.9, 39.7)	89.4 (88.1, 90.5)	2.68 (1.85, 3.86)	0.80 (0.70, 0.92)	3.34 (2.02, 5.54)
Morikawa (2004)[101]	Unspecified	Cohort	C	C	408	845	3965	17453	9.3 (8.5, 10.2)	95.4 (95.1, 95.7)	2.02 (1.80, 2.26)	0.95 (0.94, 0.96)	2.13 (1.88, 2.40)
Adenomas >1cm													
Allison (2002)[5]	FlexSure	Cohort	C	C	33	140	79	5104	29.6 (21.4, 39.0)	97.3 (96.8, 97.7)	11.07 (7.98, 15.36)	0.72 (0.64, 0.82)	15.31 (9.89, 23.70)
Gondal (2003)[108]	FlexSure	Cohort	C	S	64	225	168	4873	27.7 (22.0, 33.9)	95.6 (95.0, 96.1)	6.26 (4.91, 7.99)	0.76 (0.70, 0.82)	8.27 (6.03, 11.35)
Allison (1996)[8]	Immudia HemSp	Cohort	C	CR/FU	68	350	34	7009	66.5 (56.5, 75.5)	95.2 (94.7, 95.7)	13.97 (11.77, 16.57)	0.35 (0.27, 0.46)	39.71 (26.01, 60.62)
Nakama (2001)[73]	Immudia HemSp	Cohort	C	C	41	677	29	9141	58.5 (46.1, 70.0)	93.1 (92.6, 93.6)	8.47 (6.87, 10.44)	0.45 (0.34, 0.59)	18.98 (11.76, 30.63)
Nakama (2000)[42]	Immudia HemSp	Case-control	C	ULTE	119	8	131	242	47.6 (41.3, 54.0)	96.6 (93.6, 98.5)	14.06 (7.17, 27.57)	0.54 (0.48, 0.61)	25.93 (12.53, 53.66)
	Iatro HemCheck				116	12	134	238	46.4 (40.1, 52.8)	95.0 (91.6, 97.4)	9.32 (5.34, 16.26)	0.56 (0.50, 0.64)	16.53 (8.89, 30.74)
	LA Hemochaser				120	9	130	241	48.0 (41.7, 54.4)	96.2 (93.0, 98.2)	12.68 (6.71, 23.98)	0.54 (0.48, 0.61)	23.47 (11.73, 46.99)
	MonoHaem				117	12	133	238	46.8 (40.5, 53.2)	95.0 (91.6, 97.4)	9.40 (5.39, 16.40)	0.56 (0.50, 0.63)	16.79 (9.03, 31.23)
	OC Light				123	11	127	239	49.2 (42.9, 55.6)	95.4 (92.0, 97.6)	10.74 (6.02, 19.15)	0.53 (0.47, 0.60)	20.17 (10.62, 38.31)

LR+: Positive likelihood ratio; LR-: negative likelihood ratio; DOR: diagnostic odds ratio.
*Reference standards include C: colonoscopy, BE: barium enema, S: sigmoidoscopy, FU: follow-up, CR: referral to a cancer registry, RS: resecreening, ULTE: upper and lower tract endoscopy, singly or in combination, or NR: not reported.

4.4 Sequential FOBTs

One diagnostic case control study evaluated an unnamed guaiac FOBT and an unnamed immunochemical FOBT used sequentially for the detection of all neoplasms.[84] This study used colonoscopy to verify disease in the cases, but did not report how the disease-free status of controls was determined. The study reported a sensitivity of 29.3% (95% CI: 22%, 37.3%), specificity of 96.0% (95% CI: 93.8%, 97.6%), positive likelihood ratio of 7.31 (95% CI: 4.40, 12.15), negative likelihood ratio of 0.74 (95% CI: 0.66, 0.82) and diagnostic odds ratio of 9.92 (95% CI: 5.55, 17.73).

4.5 Comparison of guaiac and immunochemical FOBTs for the detection of all neoplasms or colorectal cancer.

4.5.1 Direct comparisons

Ten studies evaluated at least one guaiac and one immunochemical FOBT using the same stool sample for each test.[1-9, 121] Of these, only two were cohort studies.[5, 8] One cohort study used colonoscopy as the reference standard after both positive and negative FOBT results.[5] The other used colonoscopy and follow-up as the reference standard after a positive FOBT and referal to the cancer registry and follow-up after a negative FOBT.[8] Four diagnostic case control studies used colonoscopy to diagnose disease in the cases,[2, 7, 9, 10] with two also using barium enema,[2, 7] and verification of the disease-free status of the controls used colonoscopy and/or barium enema,[2, 9] upper and lower tract endoscopy,[7] or was not reported.[10] The remaining four diagnostic case control studies did not report how the disease status of cases or controls was verified.[1, 3, 4, 6]

The two diagnostic cohorts, published by the same author, compared Haemoccult Sensa with Flexsure in the detection of all neoplasms,[5] and non-rehydrated Haemoccult, Haemoccult Sensa and Immudia HemSp in the detection of colorectal cancer.[8] Both were large studies, with 4719 participants providing interpretable FOBTs and undergoing the reference standard in one study,[5] and 8104 participants that were screened with at least one FOBT in the other.[8] Only one study clearly recruited an appropriate patient spectrum,[8] the other was only published as an abstract.[5]

In one study, the guaiac FOBT, Haemoccult Sensa, was reported as being more sensitive (43.1%) and less specific (90.7%) for the detection of all neoplasms than the immunochemical FOBT, Flexsure (sensitivity 33.1%, specificity 97.5%), although both tests had low sensitivities.[5] Results are presented in figure 30. For the detection of colorectal cancer, however, FlexSure was reported as more sensitive (79.1%) and more specific (96.9%) than Haemoccult Sensa (sensitivity 63.3%, specificity 90.1%). Results are presented in figure 31. The accuracy was improved for detecting colorectal cancer for both tests compared to the detection of all neoplasms. In the other cohort study,[8] Haemoccult Sensa was reported as having the highest sensitivity for the detection of clorectal cancer, at 78.6% (specificity 86.7%), followed by the immunochemical FOBT Immudia HemSp at 68.2% (specificity 94.4%), with unrehydrated Haemoccult having the lowest sensitivity, at 37.5% (specificity 97.7%).

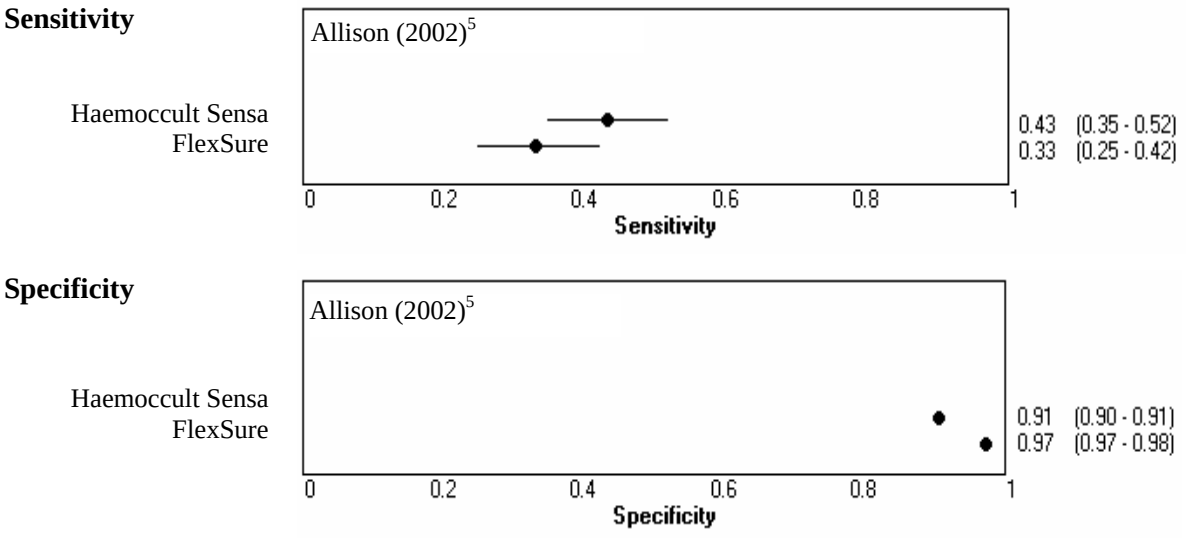


Figure 30: The sensitivity and specificity of guaiac and immunochemical FOBTs for the detection of all neoplasms, when directly compared in the diagnostic cohort study

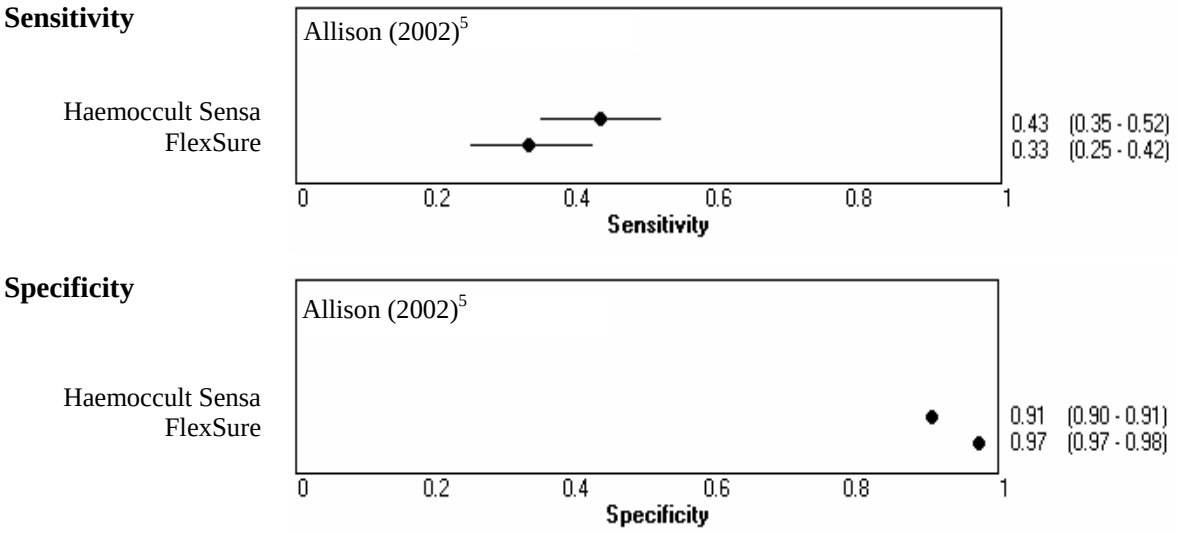


Figure 31: The sensitivity and specificity of guaiac and immunochemical FOBTs for the detection of CRC, when directly compared in the diagnostic cohort studies

Sensitivity

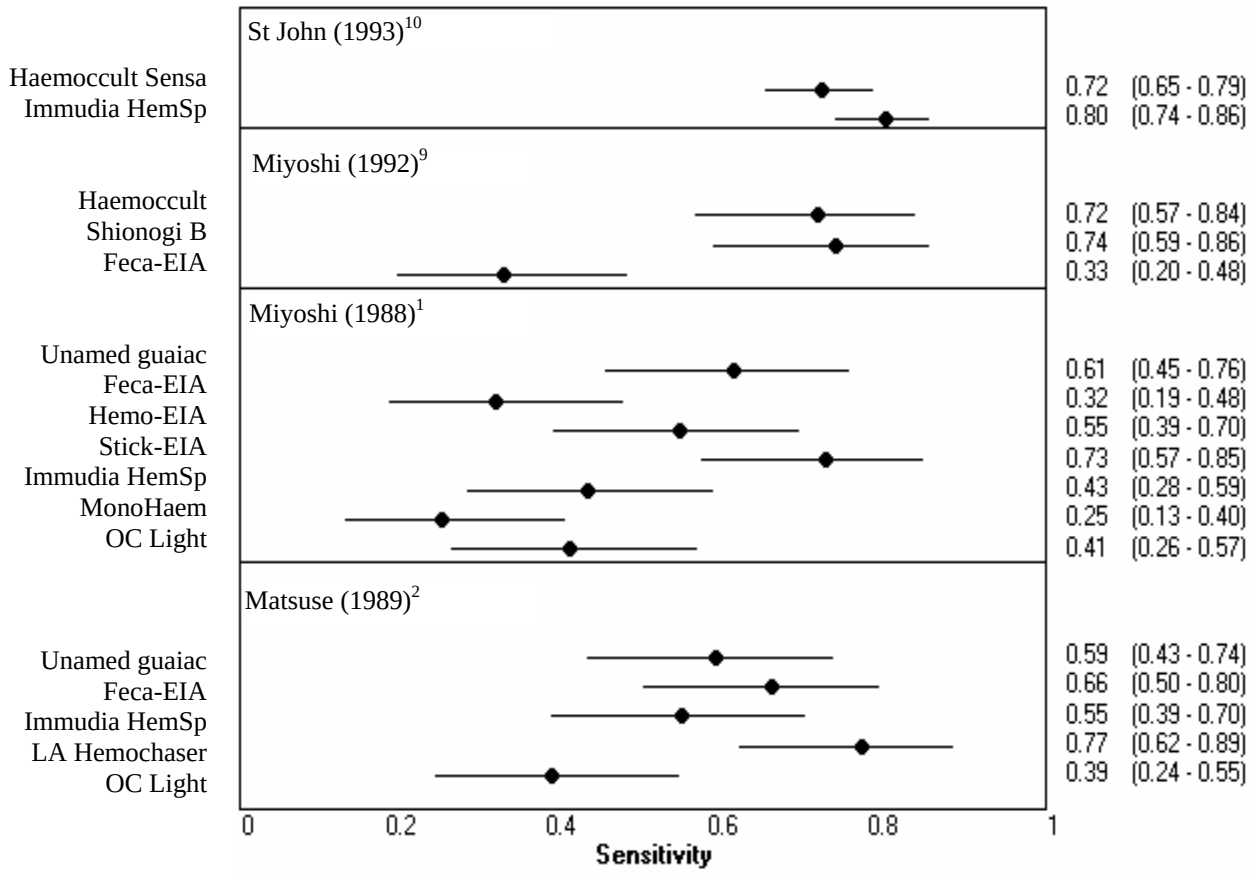


Figure 32a: The sensitivity of guaiac and immunochemical FOBTs for the detection of all neoplasms, when directly compared in the diagnostic case-control studies

The diagnostic case control studies compared either Haemoccult,[6, 7, 9] Haemoccult Sensa,[10] Shionogi B[3, 4, 9] or an unnamed guaiac FOBT[1, 2] with Immudia HemSp,[1, 2, 10] Feca-EIA,[1, 2, 6, 9] Hemo-EIA,[1] Stick-EIA,[1] MonoHaem,[1, 7] OC Light,[1, 2, 6] LA Hemochaser,[2] or Ouchterlony.[3, 4]

Four diagnostic case control studies reported on accuracy for the detection of all neoplasms.[1, 2, 9, 10] Although three of these studies reported that an immunochemical FOBT had the highest sensitivity, and all four reported an immunochemical FOBT as having the highest specificity, immunochemical FOBTs were not consistently better than guaiac FOBTs across the studies, and no one immunochemical FOBT was consitently better than the others. Results are presented in figure 32 and table 3.

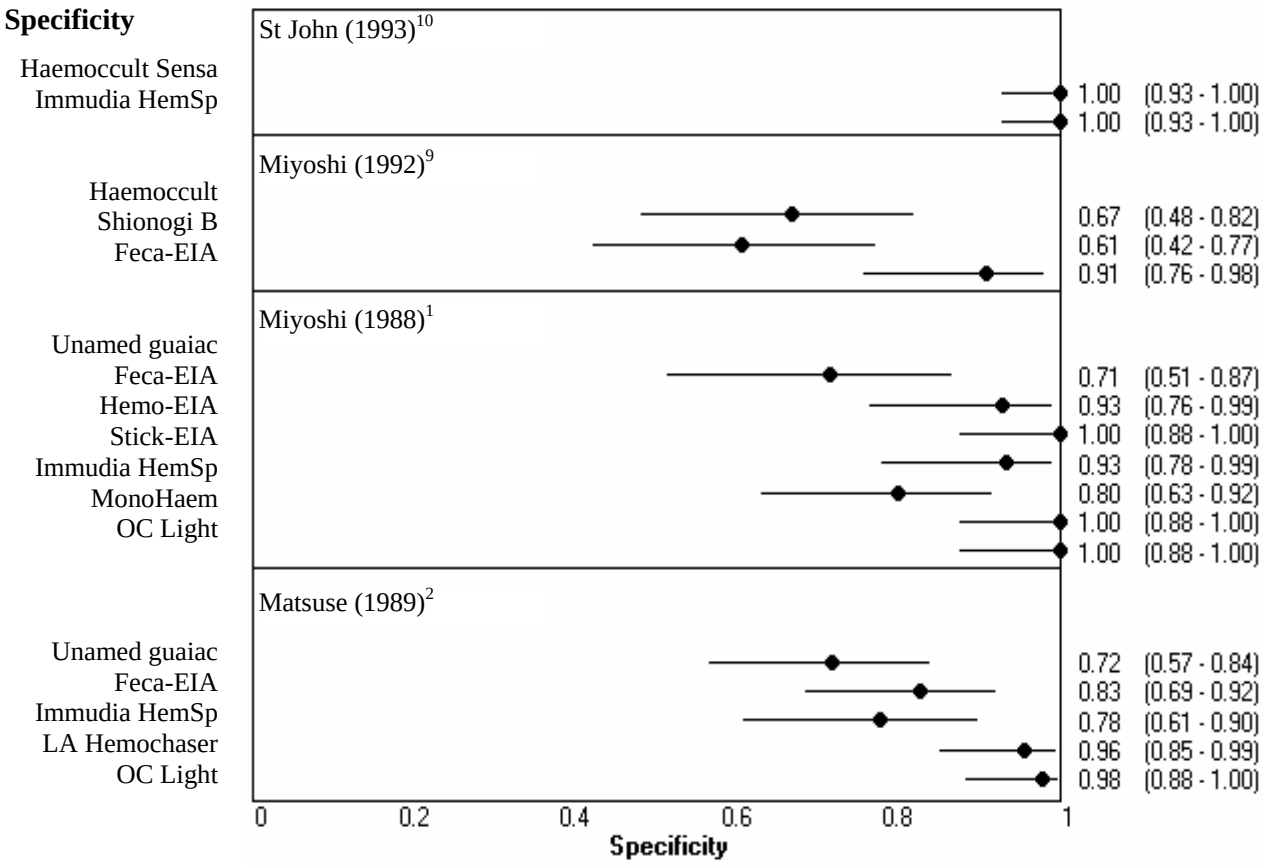


Figure 32b: The specificity of guaiac and immunochemical FOBTs for the detection of all neoplasms, when directly compared in the diagnostic case-control studies

Four diagnostic case control studies reported on accuracy for the detection of colorectal cancer.[3, 4, 6, 7] Two of the studies reported that an immunochemical FOBT had the highest sensitivity, and three reported an immunochemical FOBT had the highest specificity, with the fourth reporting that the guaiac and immunochemical FOBTs had the same specificity. No one technology, or individual test, was consistently better than the others across the studies. Results are presented in figure 33 and table 3.

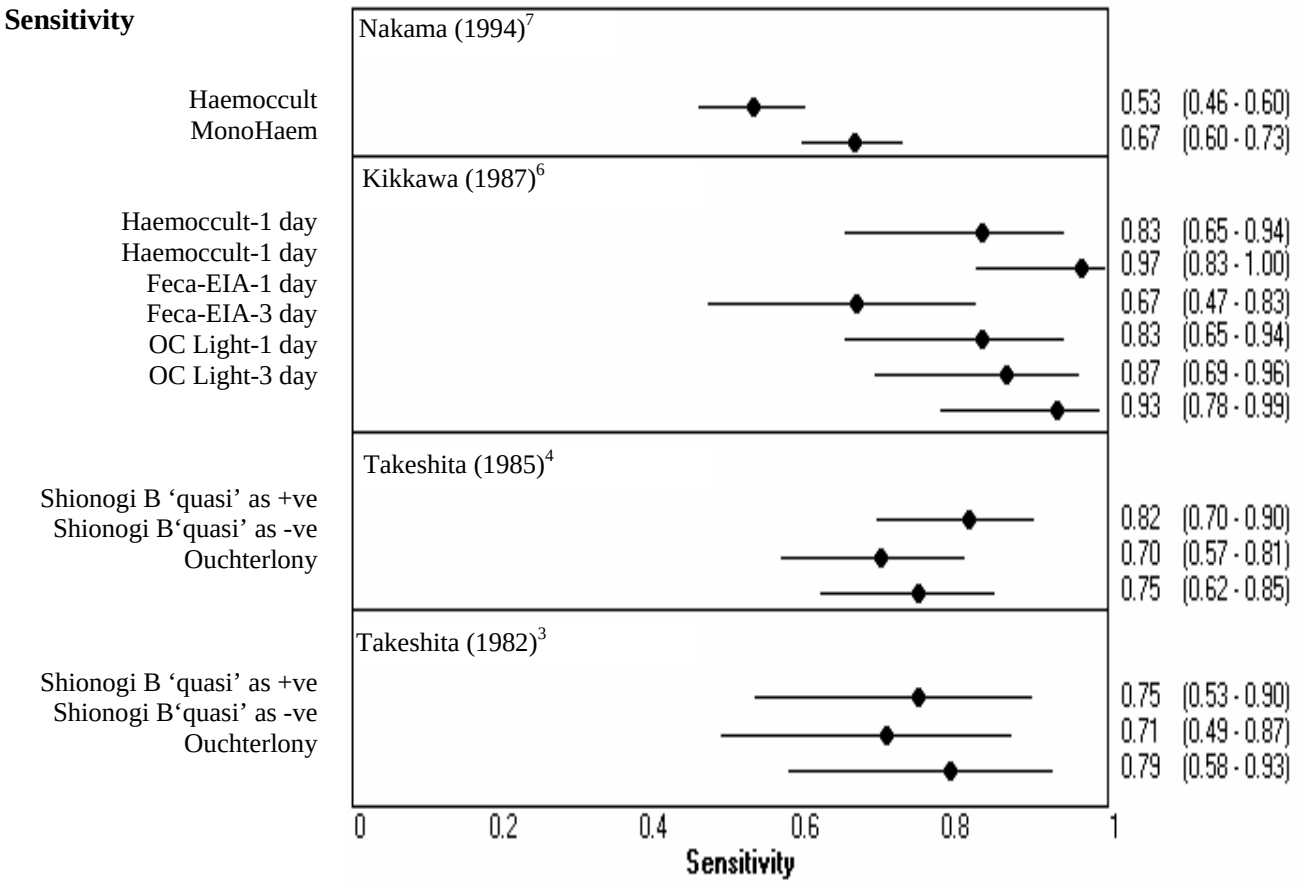


Figure 33a: The sensitivity of guaiac and immunochemical FOBTs for the detection of CRC, when directly compared in the diagnostic case-control studies

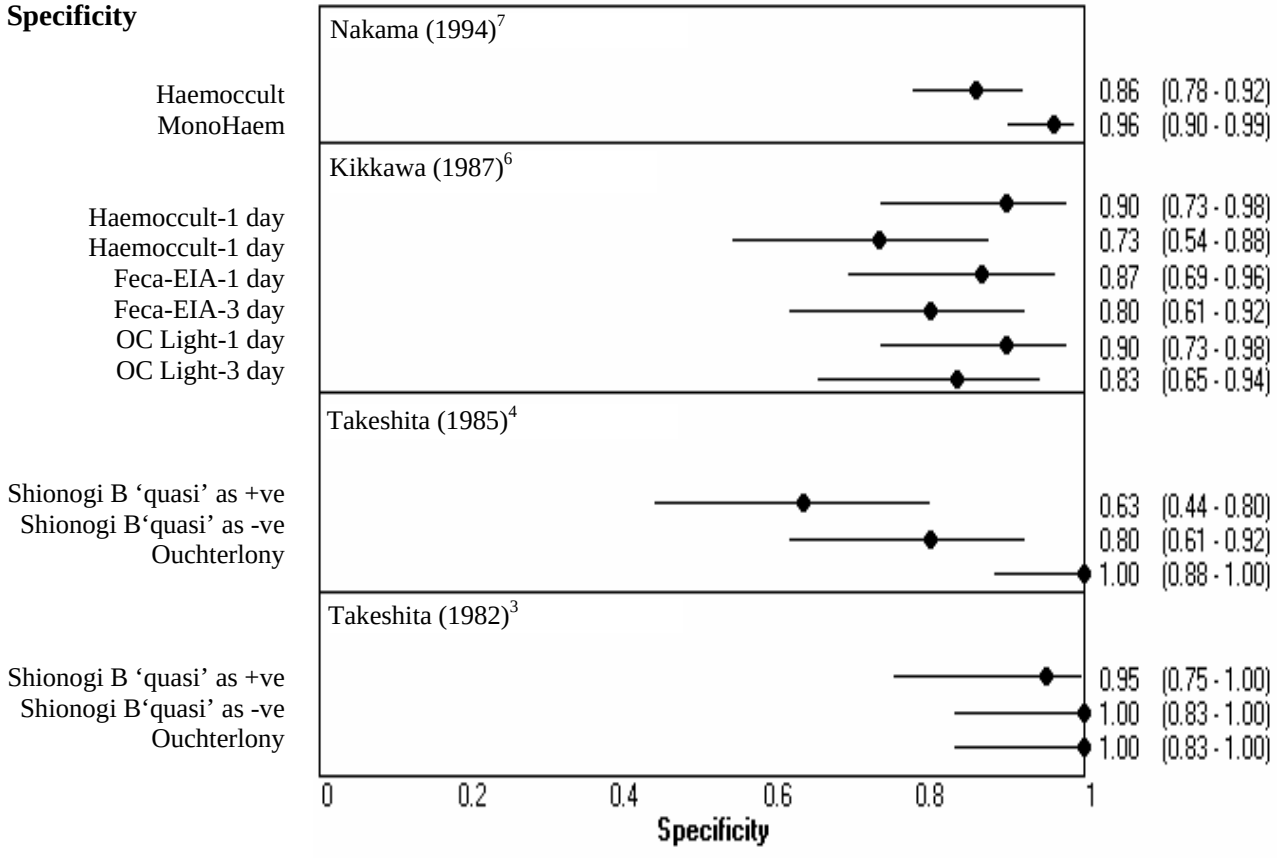


Figure 33b: The specificity of guaiac and immunochemical FOBTs for the detection of CRC, when directly compared in the diagnostic case-control studies

Table 3: Results of studies that reported direct comparisons between guaiac and immunochemical FOBTs

Study ID	Index test	Study design	Reference standard*		TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
			+ve/ case	-ve/ control									
All neoplasms													
Allison (2002)[5]	HO Sensa	Cohort	C	C	59	525	78	5137	43.1 (34.6, 51.8)	90.7 (89.9, 91.5)	4.65 (3.77, 5.72)	0.63 (0.54, 0.73)	7.41 (5.23, 10.50)
	FlexSure				40	133	81	5102	33.2 (24.9, 42.3)	97.5 (97.0, 97.9)	13.02 (9.62, 17.62)	0.69 (0.61, 0.78)	18.99 (12.55, 28.74)
Miyoshi (1992)[9]	HO	Case-control	C	C and/or BE	33	11	13	22	71.3 (56.5, 84.0)	66.2 (48.2, 82.0)	2.11 (1.27, 3.49)	0.43 (0.26, 0.72)	4.86 (1.88, 12.56)
	Shionogi B				34	13	12	20	73.4 (58.9, 85.7)	60.3 (42.1, 77.1)	1.85 (1.18, 2.90)	0.44 (0.26, 0.76)	4.19 (1.63, 10.77)
	Feca-EIA				15	3	31	30	33.0 (20.0, 48.2)	89.7 (74.4, 97.5)	3.20 (1.10, 9.37)	0.75 (0.59, 0.94)	4.29 (1.21, 15.15)
St John (1993)[10]	HO Sensa	Case-control	C	NR	136	0	52	50	72.2 (65.4, 78.6)	99.0 (92.9, 100)	73.67 (4.66, 1163.5)	0.28 (0.22, 0.35)	262.60 (15.91, 4334.1)
	Immudia HemSp				151	0	37	50	80.2 (73.8, 85.6)	99.0 (91.2, 100)	81.76 (5.18, 1290.7)	0.20 (0.15, 0.27)	408.04 (24.61, 6766.3)
Matsuse (1989)[2]	Unspecified guaiac	Case-control	C/BE	C and/or BE	26	13	18	33	59.1 (43.2, 73.7)	71.7 (56.5, 84.0)	2.09 (1.24, 3.52)	0.57 (0.38, 0.85)	3.67 (1.52, 8.83)
	Feca-EIA				29	8	15	38	65.6 (49.9, 79.1)	81.9 (68.0, 91.6)	3.62 (1.90, 6.90)	0.42 (0.28, 0.64)	8.62 (3.29, 22.61)
	Immudia HemSp				23	8	19	28	54.7 (38.8, 69.9)	77.0 (6.0, 89.2)	2.38 (1.24, 4.56)	0.59 (0.41, 0.85)	4.04 (1.53, 10.69)
	LA Hemochaser				34	2	10	44	76.7 (61.7, 88.0)	94.7 (83.9, 99.1)	14.41 (4.27, 48.67)	0.25 (0.14, 0.42)	58.49 (13.73, 249.13)
	OC Light				17	1	27	45	38.9 (24.7, 54.6)	96.8 (87.0, 99.8)	12.19 (2.42, 61.36)	0.63 (0.50, 0.80)	19.30 (3.41, 109.25)
Miyoshi (1988)[1]	Unspecified guaiac	Case-control	NR	NR	27	8	17	20	61.4 (45.5, 75.6)	71.4 (51.3, 86.8)	2.15 (1.14, 4.04)	0.54 (0.35, 0.84)	3.97 (1.43, 11.01)
	Feca-EIA				14	2	30	26	32.2 (19.1, 47.8)	91.4 (74.9, 98.5)	3.74 (1.06, 13.16)	0.74 (0.59, 0.93)	5.04 (1.19, 21.26)
	Hemo-EIA				24	0	20	28	54.4 (38.9, 69.4)	98.3 (85.0, 100)	31.58 (2.00, 499.32)	0.46 (0.34, 0.64)	68.12 (3.91, 1185.8)
	Stick-EIA				32	2	12	28	72.2 (56.9, 84.5)	91.9 (76.4, 98.6)	8.96 (2.69, 29.80)	0.30 (0.19, 0.49)	29.64 (6.97, 126.11)
	Immudia HemSp				19	7	25	28	43.3 (28.6, 58.9)	79.2 (62.4, 90.9)	2.08 (1.01, 4.27)	0.72 (0.53, 0.97)	2.91 (1.07, 7.88)
	MonoHaem				11	0	33	28	25.6 (13.7, 40.7)	98.3 (85.0, 100)	14.82 (0.91, 241.97)	0.76 (0.63, 0.91)	19.57 (1.10, 346.89)
	OC Light				18	0	26	28	41.1 (26.7, 56.8)	98.3 (85.0, 100)	23.84 (1.49, 380.52)	0.60 (0.47, 0.77)	39.79 (2.28, 693.72)

CRC													
Allison (1996)[8]	HO	Cohort	C/FU	CR/FU	13	185	22	7845	37.5 (21.5, 55.1)	97.7 (97.3, 98.0)	16.24 (10.40, 25.34)	0.64 (0.50, 0.82)	25.38 (12.73, 50.61)
	HO Sensa				27	1046	7	6824	78.6 (62.1, 91.3)	86.7 (85.9, 87.5)	5.91 (4.93, 7.09)	0.25 (0.13, 0.47)	23.91 (10.64, 53.75)
	Immudia HemSp				22	418	10	7043	68.2 (49.7, 83.2)	94.4 (93.8, 94.9)	12.16 (9.46, 15.63)	0.34 (0.21, 0.56)	36.07 (17.22, 75.52)
Allison (2002)[5]	HO Sensa	Cohort	C	C	9	575	5	5210	63.3 (35.1, 87.2)	90.1 (89.3, 90.8)	6.37 (4.30, 9.43)	0.41 (0.21, 0.79)	15.64 (5.45, 44.85)
	FlexSure				9	164	2	5181	79.2 (47.1, 96.4)	96.9 (96.4, 97.4)	25.73 (18.55, 35.68)	0.21 (0.07, 0.65)	119.69 (29.46, 486.26)
Nakama (1994)[7]	HO	Case-control	C/BE	ULTE	106	14	94	86	53.0 (45.8, 60.1)	85.6 (77.6, 92.1)	3.69 (2.25, 6.05)	0.55 (0.46, 0.65)	6.72 (3.61, 12.51)
	MonoHaem				133	4	67	96	66.4 (59.4, 72.9)	95.5 (89.5, 98.6)	14.91 (6.01, 36.98)	0.35 (0.29, 0.43)	42.41 (15.77, 114.09)
Kikkawa (1987)[6]	HO-1 day	Case-control	NR	NR	25	3	5	27	83.3 (65.3, 94.4)	90.0 (73.5, 97.9)	8.33 (2.82, 24.67)	0.19 (0.08, 0.416)	45.00 (9.73, 208.08)
	Feca-EIA-1 day				20	4	10	26	66.7 (47.2, 82.7)	86.7 (69.3, 96.2)	5.00 (1.94, 12.887)	0.39 (0.23, 0.65)	13.00 (3.55, 47.60)
	OC Light-1 day				26	3	4	27	85.5 (68.2, 95.5)	88.7 (72.2, 97.2)	7.57 (2.79, 20.53)	0.16 (0.07, 0.39)	46.27 (10.37, 206.39)
	HO-3 days				29	8	1	22	95.2 (82.8, 99.9)	72.6 (54.1, 87.7)	3.47 (1.95, 6.19)	0.07 (0.01, 0.32)	52.06 (8.43, 321.43)
	Feca-EIA-3 days				25	6	5	24	82.3 (64.4, 93.6)	79.0 (60.7, 91.5)	3.92 (1.94, 7.92)	0.22 (0.10, 0.49)	17.48 (4.94, 61.84)
	OC Light-3 days				28	5	2	25	93.3 (77.9, 99.2)	83.3 (65.3, 94.4)	5.60 (2.51, 12.54)	0.08 (0.02, 0.31)	70.00 (12.47, 393.36)
Takeshita (1985)[4]	Shionogi B 'quasipositives' as positive	Case-control	NR	NR	49	11	11	19	81.7 (69.6, 90.5)	63.3 (43.9, 80.1)	2.23 (1.37, 3.62)	0.29 (0.16, 0.53)	7.69 (2.86, 20.70)
	Shionogi B 'quasipositives' as negative				42	6	18	24	69.7 (56.8, 81.2)	79.0 (61.4, 92.3)	3.32 (1.65, 6.71)	0.38 (0.25, 0.59)	8.66 (3.11, 24.08)
	Ouchterlony				45	0	15	30	74.6 (61.8, 84.9)	98.4 (85.9, 100)	46.25 (2.95, 725.78)	0.26 (0.17, 0.40)	179.06 (10.32, 3105.8)
Takeshita (1982)[3]	Shionogi B 'quasipositives' as positive	Case-control	NR	NR	18	1	6	19	75.0 (53.3, 90.2)	95.0 (75.1, 99.9)	15.00 (2.19, 102.75)	0.26 (0.31, 0.53)	57.00 (6.23, 521.15)
	Shionogi B 'quasipositives' as negative				17	0	7	20	70.0 (48.9, 87.4)	97.6 (83.2, 100)	29.40 (1.88, 460.18)	0.31 (0.17, 0.56)	95.67 (5.09, 1796.9)
	Ouchterlony				19	0	5	20	78.0 (57.1, 91.9)	97.6 (79.8, 100)	32.76 (2.10, 510.67)	0.23 (0.11, 0.47)	145.36 (7.53, 2807.2)

LR+: Positive likelihood ratio; LR-: negative likelihood ratio; DOR: diagnostic odds ratio.
*Reference standards include C: colonoscopy, BE: barium enema, S: sigmoidoscopy, FU: follow-up, CR: referral to a cancer registry, ULTE: upper and lower tract endoscopy, singly or in combination, or NR: not reported.

4.5.2 Indirect comparisons

This section provides an overview of those studies that evaluated only guaiac or immunochemical FOBTs (results are plotted in ROC space).

4.5.2.1 All neoplasms

Twelve diagnostic cohorts evaluated the diagnostic accuracy of only guaiac FOBTs[64-68, 70, 77, 78, 80, 97, 101, 113] and five only immunochemcial FOBTs[46, 71, 73, 96, 108] for the detection of all neoplasms. Overall, there was no clear indication that either guaiac or immunochemical FOBTs performed better. Sensitivity ranged from 6.2% (unrehydrated Haemoccult, specificity 98.0%) to 83.3% (KryptoHaem, specificity 98.4%) for the guaiac FOBTs, and from 5.4% (OC Light, specificity 98.5%) to 62.3% (Immudia HemSp, specificity 94.3%) for the immunochemical FOBTs. Specificity ranged from 65.0% (unnamed, sensitivity 44.1%) to 99.0% (unrehydrated Haemoccult, sensitivity 19.3%) for the guaiac FOBTs, and from 89.4% (SPA Test, sensitivity 30.3%) to 98.5% (OC Light, sensitivity 5.4%) for the immunochemical FOBTs. Figure 34 shows the comparison between tests.

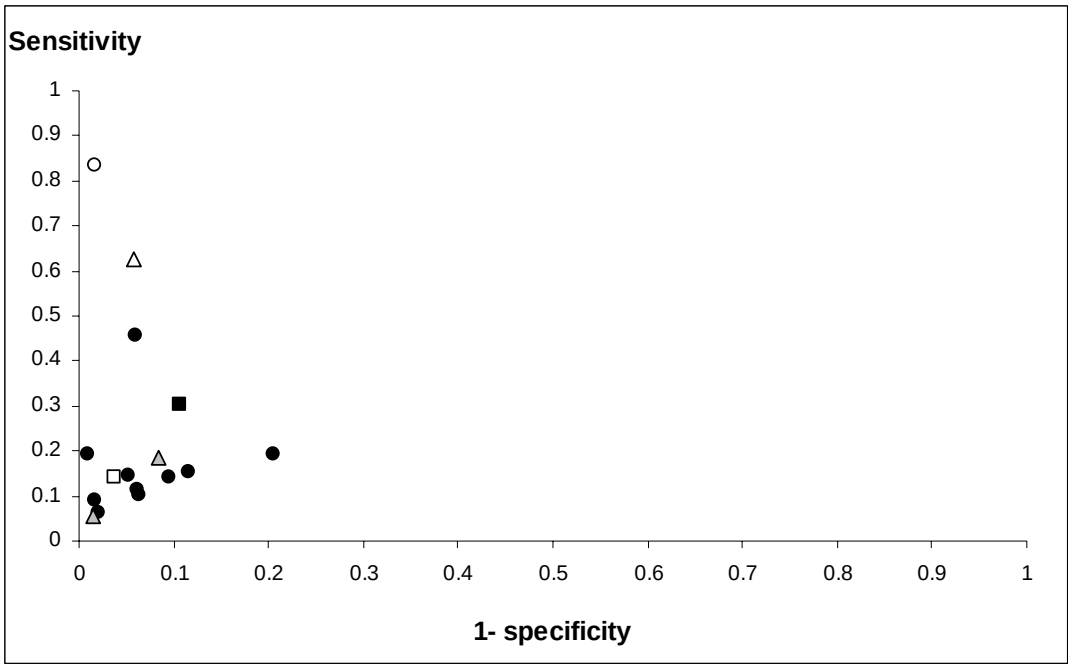


Figure 34: ROC Guaiac (circles) Immunochemical (triangles and squares), Haemoccult (●), KryptoHaem (○), Shionogi B (◎), OC Light (△), Immudia HemSp (△), MonoHaem (▲), SPA test (■) and Flexsure (□)

Three diagnostic case-control studies evaluated the diagnostic accuracy of only guaiac FOBTs[79, 81, 83] and six evaluated only immunochemcial FOBTs[46, 86, 88, 89, 91, 92] for the detection of all neoplasms.

For the detection of all neoplasms, case control-studies reported sensitivity ranging from 47.4% (KryptoHaem, specificity 98.3%) to 65.2% (Haemoccult, specificity 99.0%) for the guaiac FOBTs, and from 45.7% (OC Light, specificity 94.3%) to 97.7% (Immudia HemSp, specificity 98.8%) for the immunochemical FOBTs. Specificity ranged from 50% (Haemoccult, sensitivity 50%) to 99.0% (Haemoccult, sensitivity 65.1%) for the guaiac FOBTs, and from 91.7% (MonoHaem, sensitivity 69.7%) to 99.0% (Immudia HemSp, sensitivity 87.5%) for the immunochemical FOBTs. Overall, there was no clear indication that either guaiac or immunochemical FOBTs performed better. Immudia HemSp appeared to have the best overall accuracy of any FOBT evaluated for the detection of all neoplasms. Figure 35 shows the comparison between tests.

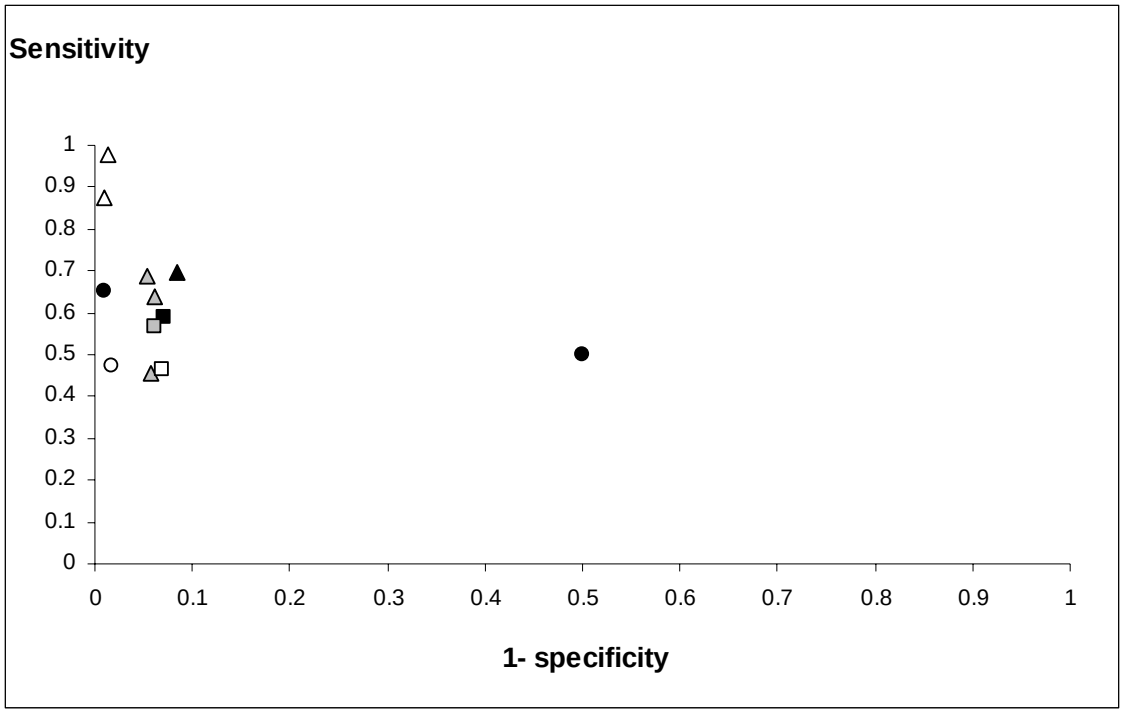


Figure 35: ROC Guaiac (circles) Immunochemical (triangles and squares), Haemoccult (●), KryptoHaem (○), OC Light (△), Immudia HemSp (△), MonoHaem (▲), SPA test (■), Feca-EIA (□) and Iatro HemCheck (▢)

4.5.2.2 CRC

Eighteen diagnostic cohort studies evaluataed the diagnostic accuracy of only guaiac FOBTs[64, 65, 67, 69, 70, 72, 80, 93, 94, 97, 100, 101, 105-107, 110, 112, 113] and thirteen evaluated only immunochemcial FOBTs[46, 71, 73-76, 95, 96, 98, 99, 102, 103, 108] for the detection of CRC. No indirect comparison could be made using diagnostic case-control studies as none evaluated only a guaiac FOBT.

Overall, there was no clear indication that either guaiac or immunochemical FOBTs performed better, and no single test appeared to perform better than others. The inconsistencies in the results between studies can be seen from the results for unrehydrated Haemoccult, which had both the highest and lowest, sensitivities and specificities reported for the guaiac FOBTs. Sensitivity ranged from 25.0% (specificity 98.7%) to 96.2% (specificity 99.2%) and specificity ranged from 80.0% (sensitivity 30.0%) to 99.2% (sensitivity 96.1%). The other guaiac FOBTs that were evaluated included Haemoccult Sensa (sensitivity 62.2%, specificity 95.5%), Shionogi B (sensitivity 26.8%, specificity 94.1%), and an unnamed guaiac FOBT (sensitivity 66.7%, specificity 94.5%). Further highlighting the inconsistencies in the results between studies, MonoHaem had both the highest, and the second lowest reported sensitivity of all the immunochemical tests. For the immunochemical FOBTs, sensitivity ranged from 1.7% (FlexSure, specificity 94.6%) to 98% (MonoHaem, specificity 95.9%) and specificity from 88.8% (Spa Test, sensitivity 50.0%) to 99.9% (MonoHaem, sensitivity 6.7%). Figure 36 shows the comparison between tests.

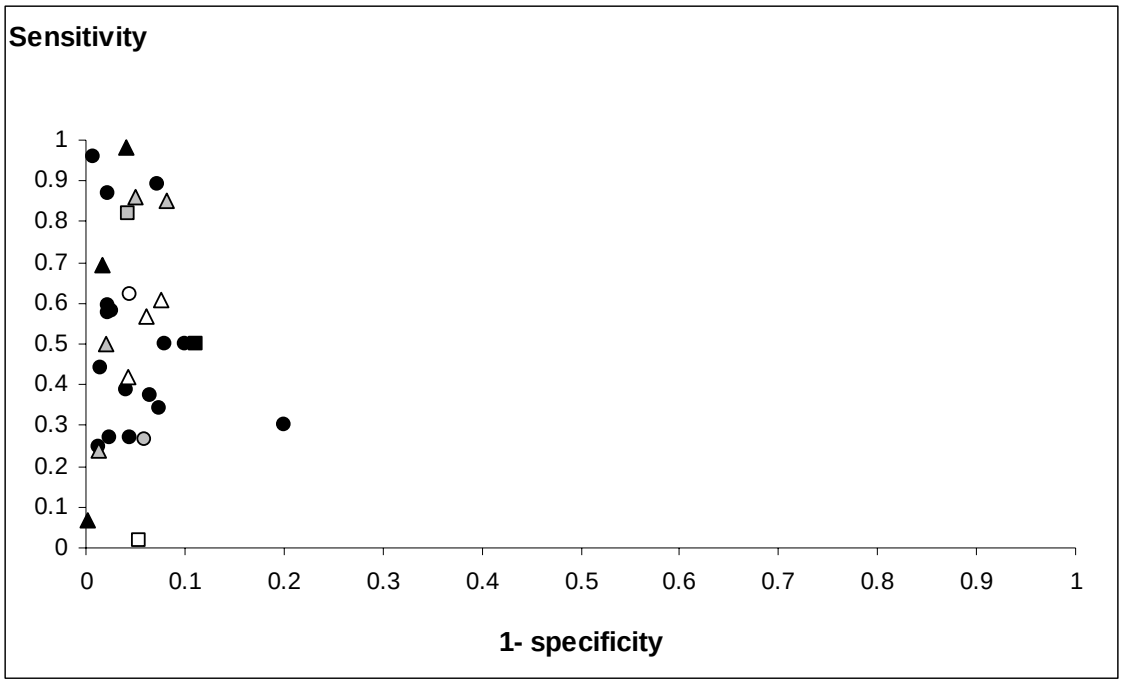


Figure 36: ROC Guaiac (circles) Immunochemical (triangles and squares), Haemoccult (●), Haemoccult Sensa (○), Shionogi B (◍), OC Light (△), Immudia HemSp (△), MonoHaem (▲), SPA test (■), Flexsure (□) and Iatro HemCheck (▣)

4.6 Adverse events

Three papers reported the impact of screening on daily life and levels of anxiety after a positive FOBT result.[104, 109, 111] Outcomes measured included psychiatric morbidity, anxiety, distress, worry, and the affect on daily life. One RCT conducted in the UK, randomly allocated 152 850 people aged between 45 and 74 years to either screening with a guaiac FOBT or no screening, to determine whether screening an average risk population with a guaiac FOBT would reduce mortality.[28] From this population, the general health questionnaire was sent to 2184 people before screening and 1693 people after screening to investigate psychiatric morbidity.[104] 843 people completed both questionnaires. A score of five or more on the GHQ was considered to indicated probable psychiatric morbidity. No difference was reported in the proportion of people scoring five or more, before and three months after FOBT was offered. For people with a false positive FOBT, the highest anxiety levels occurred after notification of a positive test and before colonoscopy. The lowest level of anxiety was experienced the day after colonoscopy and this remained low one month later.

Another RCT conducted in Sweden randomised 68 308 people aged between 60 and 64 years to either screening with a guaiac FOBT or no screening, to determine the prevalence of colorectal neoplasms in the two groups.[122] During this study, 3548 people who were invited for screening, completed a questionnaire to assess the degree of worry engendered by screening.[109] Forty six percent were worried by the invitation, and refused to participate, and of these, 15% were 'extremely' worried. Sixteen percent of those who participated in the screening reported being 'extremely' worried. For people with a negative FOBT, 19% experienced severe worry, and of these 18% said that their daily life was negatively affected. For people with an initial positive FOBT, 60% experienced severe worry, and 38% said there daily life was negatively affected.

A third RCT (conducted in the UK to investigate compliance with different methods of colorectal cancer screening) reported the concern of people aged 40-75 years receiving a false positive FOBT, and the impact of dietary restrictions (applied during the test) on their daily lifes.[111] Fifty-six people had a false positive FOBT, of whom 54 completed a questionnaire. Of these, 68% reported experiencing distress, (62% of these slight distress, 24% moderate distress, and 14% very distressed). Sixty nine percent reported being worried that they may have cancer, and of these 68% reported experiencing slight distress, 24% moderate distress, and 8% were very distressed. Forty three

percent of people found the dietary restrictions slightly disruptive, 6% moderately disruptive and 4% very disruptive. Delays in the process caused slight worry for 26% of people, moderate worry for 6%, and 4% were very worried.

4.7 Economic evaluations

Seven full economic evaluations met the inclusion criteria. Two were conducted in the UK,[114, 115] one in the USA,[116] one in Italy,[117] one in France,[118] one in Japan,[119] and one in Singapore.[120] One study evaluated two guaiac FOBTs,[114] whereas the others evaluated at least one guaiac and one immunological FOBT.

Four of the studies modelled a hypothetical cohort of people.[116, 118-120] Three studies evaluated the cost of screening for cancers only,[114, 115, 120] whereas the other four specified costs for cancer and adenomas. The guaiac FOBTs evaluated included Haemoccult[114, 115, 117, 118] or Haemoccult II,[116] Haemoccult Sensa,[116] Okokit,[114] and Coloscreen.[115] The immunochemical FOBTs evaluated included Immudia HemSp,[115, 117] Feca-EIA,[115] EZ-detect,[115] and Magstream HemSp.[118] Two studies evaluated a guaiac and an immunochemical FOBT, but did not specify which tests these were.[119, 120] Another study specified the guaiac FOBTs as Haemoccult and Haemoccult Sensa, but didn't specify the immunochemical test used.[116] All economic evaluations identified were cost-effectiveness analyses (CEA). Each economic evaluation was abstracted and these presented in full in Appendix K.

The health outcomes reported in the studies varied. Three studies reported life years saved,[116, 118, 119] one life expectancy,[120] and three cost per case detected.[114, 115, 117] Of these, the number of life years saved is considered a better outcome measure. Number of cases detected is an appropriate outcome measure for the purpose of screening. Studies evaluating the detection of cancer and adenomas separately, rather than just cancer, were considered to be better, as detecting adenomas will be important for any screening programme.

The perspectives of the evaluations included in the review were those of the health service,[115, 117] the payer,[114, 116, 119] the French social service,[118] or were not reported.[120] Details of the included economic evaluations are given in Tables 4 to 18.

4.7.1 Guaiac FOBTs

In this section the results for named guaiac tests are presented. Results from the studies that evaluated guaiac FOBTs, but did not name the specific test, are included only in the section on intra-study comparisons between guaiac and immunochemical FOBTs.

4.7.1.1 Haemoccult

Four studies evaluated Haemoccult,[114, 115, 117, 118] and one evaluated Haemoccult II.[116] One study reported the cost per case detected using re-hydrated Haemoccult in people aged 50-70 as $12 900 for CRC, $2,200 for adenomas, and $4,530 for adenomas over 9mm in size.[117] The same study reported that the cost per case detected substantially increased in people aged 40-49, being $23,930 for CRC, $7,990 for adenomas, and $35,980 for adenomas over 9mm in size.

A second study compared the use of Haemoccult without re-hydration, and testing on samples from three or six successive days, with no re-testing regardless of FOBT result.[115] The cost per cancer detected for the three-days method was £2,814 (sensitivity 67%, specificity 97%) and for the six-days method £3,156 (sensitivity 74%, specificity 99%). When Haemocult slides were re-hydrated the cost per cancer detected for the three-day method increased to £3,456 (sensitivity 72%, specificity 95%). The number of re-tests that were undertaken also affected the cost per cancer detected, with a reduction in the cost of the three-day method to £2,202 when all first round positive FOBTs were re-tested to confirm positivity. The cost per cancer detected dropped to £2,116 when those that were negative on the second round of testing had a third FOBT.

A third study reported that the cost of screening, per person, with Haemoccult for 10 years was €195, with 9.8 life years saved in a cohort of 165,000 people, and €179 on a 20 year programme, with 16.7 life years saved.[118]

The fourth study reported a cost per case detected when screening started at 40 years of age, of £16,411.[114]

The Haemoccult II study reported that the average cost per life year gained was $1,071 (sensitivity of 40%, specificity of 98%, test cost $4.50).[116] This increased to $2,245 when screening was repeated every three years.

4.7.1.2 Haemoccult Sensa
One study evaluated Haemoccult Sensa and reported that the average cost per life year gained was $3,342 (sensitivity of 70%, specificity of 92.5%, test cost $4.50).[116] This increased to $5,827 per life year gained when the cost of the test was increased to $28.

4.7.1.3 Okokit
One study evaluated Okokit and reported a cost per CRC case detected as £15,881 when screening was started at the age of 40, (sensitivity 55%, prevalence of positive results 5%).[114] When sensitivity was increased to 90%, and prevalence of positive results remained 5%, the cost per CRC case detected dropped to £9,704. When specificity was increased, and prevalence decreased from 5% to 1.5%, the cost per CRC case detected again dropped, to £5,049.

4.7.1.4 Coloscreen
One study evaluated Coloscreen and reported a cost per cancer detected of £6,910 with Coloscreen (sensitivity of 33%, specificity of 94%, test cost £1.00).[115]

4.7.2 Comparisons between guaiac FOBTs
It seems inappropriate to compare the different studies reporting costs for guaiac tests because of the heterogeneity between outcomes measured, sensitivities and specificities used, the stage of disease being detected, the country the study was conducted in and year of publication, and the age range of the screening cohorts.

One study compared the cost per case detected for two guaiac FOBTs, with screening starting at the age of 40 years.[114] This intra-study comparison is presented in tabular form to assist interpretation (Table 4).

Table 4: Costs comparison per CRC detected with two guaiac FOBTs[114]

FOBT	Sensitivity	Prevalence of +veFOBT	Test cost (£)	Cost per cancer detected (£)
Haemoccult	Not reported	Not reported	12.00	16,411
Okokit	55%	5%	3.00	15,881
Okokit	90%	5%	3.00	9,704
Okokit	Unclear	1.5%	3.00	5,049

4.7.3 Immunochemical FOBTs
In this section, only the results for named immunochemical are reported. Results from the studies that did not name the specific immunochemical FOBT evaluated, are included only in the section on intra-study comparisons between guaiac and immunochemical FOBTs.

4.7.3.1 Immudia/Magstream HemSp
Two studies evaluated Immudia HemSp,[115, 117] and a third evaluated Magstream HemSp.[118] One study evaluating Immudia HemSp reported a cost per cancer detected of £5,356 (sensitivity of 95%, specificity of 93%, test cost £6.00).[115] The other study of Immudia HemSp reported the cost per case detected when tests were considered certain or borderline positives.[117] This study reported a cost per case detected in people aged 50-70 of $9,020 for CRC, $2,180 for adenomas, and $3,960 for adenomas over 9mm in size when positives were certain. These costs changed when both certain and borderline positives were followed up, with the cost per case detected for CRC rising slightly to $10,000, and the costs to detect adenomas falling slightly to $1,780 for all adenomas, and $3,730 for adenomas over 9mm. The same study reported that the cost per case detected substantially increased in people aged 40-49, being $20,220 for CRC, $12,130 for adenomas, and $20,220 for adenomas over 9mm in size when certain positives were followed up, and $14,700 for CRC, $7,350 for adenomas, and $14,700 for adenomas over 9mm in size when certain and borderline positives were followed up. The study evaluating Magstream HemSp reported the cost of screening per person

with Magstream HemSp on a 10 year programme as €151, with 9.8 life years gained in a cohort of 165 000 people, and €238 on a 20 year programme, with 16.7 life years gained.[118]

4.7.3.2 Feca-EIA
One study evaluated Feca-EIA[115] and reported a cost per cancer detected of £6,373 (sensitivity of 67%, specificity of 91%, test cost £3.00).[115]

4.7.3.3 EZ-Detect
One study evaluated EZ-detect[115] and reported a cost per cancer detected of £9,869 (sensitivity of 36%, specificity of 89%, test cost £1.00).[115]

4.7.3.4 Comparison of the immunochemical FOBTs
As with the guaiac tests, the heterogeneity between the studies reporting costs for immunochemical tests with respect to outcomes reported, perspective taken, sensitivities and specificities used, stage of disease being detected, the country the study was conducted in and year of publication , and age range of the screening cohorts, make cross-study comparisons inappropriate.

One study evaluated more than one immunochemical FOBT,[115] and the results of this intra-study comparison are presented in tabular form to assist interpretation (Table 5).

Table 5: Cost comparisons per of CRC case detected in £ sterling for three immunochemical FOBTs[115]

FOBT	Sensitivity	Specificity	Test cost	Positives	Cancers detected	Total cost (£ million)	Cost per cancer detected
Immudia HemSp	0.95	0.93	6.00	4 051	192	1.03	5,356
Feca-EIA	0.67	0.91	3.00	5 319	136	0.86	6,373
EZ-detect	0.36	0.89	1.00	9 495	112	1.11	9,869

4.7.4 Comparison of guaiac and immunochemical FOBTs
As cross-study comparisons seem inappropriate, only intra-study comparisons between guaiac and immunochemical cost effectiveness are reported. These are presented in tabular form to assist interpretation (Tables 6 to 10).

Table 6: Comparisons of costs per case detected in a screening population of 50-70 year olds in US $ between Haemoccult and Immudia HemSp[117]

	Haemoccult	Immudia HemSp	
		Positive results only	Positive and borderline results
CRC	12,900	9,020	10,000
Adenomas	2,200	2,180	1,780
Adenomas >9mm	4,530	3,860	3,730

Table 7: Comparisons of costs per CRC case detected in £ sterling between Haemoccult, Coloscreen, Immudia HemSp, Feca-EIA and EZ detect[115]

	Sensitivity	Specificity	Test cost	Cost per CRC detected
Haemoccult: 3 day, no re-hydration or retesting	67%	97%	1.70	2,814
Haemoccult: 3 day, no re-hydration. First round positives retested	58%	99%	1.80	2,202
Haemoccult: 3 day, no re-hydration. First round positives retested, and negative retests given a 3rd test	65%	99%	1.85	2,116
Haemoccult: 3 day, re-hydrated. No retesting	72%	95%	1.80	3,456
HO 6 day: no re-hydration, no retesting	74%	99%	3.40	3,156
Coloscreen	33%	94%	1.00	6,691
Immudia HemSp	95%	93%	6.00	5,356
Feca-EIA	67%	931%	3.00	6,373
EZ-detect	36%	89%	1.00	9,869

Table 8: Comparisons of costs per life year saved in US $ between Haemoccult II (HO II), Haemoccult Sensa (HO Sensa) and an unnamed immunochemical FOBT (iFOBT) followed by colonoscopy[116]

Test	Sensitivity	Specificity	Test cost	Average cost per life year gained
HO II	40	98	4.50	1,071
HO Sensa	70	92.5	4.50	3,342
iFOBT	70	98	4.50	357
iFOBT	70	95	4.50	1,994
HO Sensa	70	92.5	28	5,827
iFOBT	70	98	28	2,834
iFOBT	70	95	28	4,479
Increased surveillance to every 3 years				
HO II	40	98	4.50	2,245
iFOBT	70	98	4.50	1,830
iFOBT	70	98	28	4,161
iFOBT	70	95	4.50	3,378
iFOBT	70	95	28	5,716

Estimated discounted costs for 1 million people ranged from $197 556 566 to $453 629 724 for HO II, $775 643 892 to 1 352 544 256 for HO Sensa and $83 110 600 to 1 398 580 548 for the immunochemical FOBT depending on the moel assumptions.

Table 9: Comparisons of the incremental cost per life year saved in Singapore $ between an unnamed guaiac and unnamed immunochemical FOBT with no screening[120]

Age	Guaiac FOBT	Immunochemical FOBT
50-54	288.33	623.12
55-59	145.70	342.75
60-64	65.42	177.69
65-69	18.89	62.03

Sensitivity: Guaiac: 10% polyps, 60% CRC; immunochemical FOBT: 40% polyps and 90% CRC; Specificity: Guaiac: 90% polyps and CRC. immunochemical FOBT: 95% polyps and CRC

Table 10: Comparisons of the cost per life year saved in US $ between an unnamed guaiac and unnamed immunochemical FOBT[119]

	$
Guaiac followed by colonoscopy	28,500
Immunochemical followed by colonoscopy	13,100

Table 11: Characteristics of included economic evaluations

	Daniels (1995)[114]	Castiglione (1997)[117]	Walker (1992)[115]	Shimbo (1994)[119]	Berchi (2004)[118]	Wong (2004)[120]	van Ballegooijen (2003)[116]
Aim	Decide age at which screening should start	Compare 1 day RPHA and 3 day HO	Compare screening with no screening	Assess alternative mass screening strategies	Cost effectiveness of Magstream vs. HO	Cost effectiveness of 5 strategies for ID of CRC compared to no screening	Cost effectiveness of 3 strategies for ID of CRC compared to no screening
Population	30+	24 282 people 40-70	Hypothetical cohort of 100 000 people 50+	Hypothetical cohort of 100 000 people 40+	Hypothetical cohort of 165 000 people 50-74	Hypothetical cohort 50-70	Hypothetical cohort of 1000 000 people 65-79
Country	UK	Italy	UK	Japan	France	Singapore	USA
FOBTs used	HO Okokit (guaiac)	HO RPHA	HO Hemoquant HemeSelect Feca-EIA Coloscreen EZ-Detect	Unnamed guaiac and immunochemical	HO Magstream	Unnamed guaiac and immunochemical	HO II HO Sensa Unnamed immunochemical
Benefit	Cost per CRC case detected	Cost per person with CRC/adenoma detected	Cost per CRC case detected	Life years saved CRC and adenomas	Life years saved CRC and adenomas	Life expectancy CRC	Life years saved CRC and adenomas
Perspective	Payer	Health Service	Health Service	Payer	French Social Security Service	Not reported	Third-party payer
Direct costs	FOBT Personal costs of testing Cost of follow up	Staff General expenses Buildings Recruitment into study Assessment	Unclear – data derived from previous study	FOBT Follow up Complications Treatment	Test purchase Distribution Revelation Colonoscopy Treatment	Screening procedure Complications Treatment	Test Follow-up Surveillance Treatment
Indirect costs	None reported	None reported	None reported	None reported	None reported	None reported	None reported
Result	**See Table 12 below**	**See Table 13 below**	**See Table 14 below**	**See Table 15 below**	**See Table 16 below**	**See Table 17 below**	**See Table 18 below**
Authors Conclusion	Most cost-effective age to start was 40	Immunological FOBT more cost effective	Immudia HemSp 3 day and HO 3 day with 2 retests were the most cost-effective	Immunological FOBT every 2 years followed by colonoscopy after a positive test was more cost effective, starting at the age of 45 years	Substituting Haemoccult with Magstream was cost-effective strategy	All screening methods improved patient survival, but guaiac FOBT offered most acceptable cost-effectiveness ratio	Both guaiac and Immuno cost effective strategies for screening 65-79 year olds with no previous screening.

RPHA: Reverse passive haemagglutination (FOBT); HO: Haemoccult; HO II: Haemoccult, HO Sensa: Haemoccult SENSA; ID: identification; CRC: colorectal cancer; LYS: life years saved; CEA: cost-effectiveness analysis; RCT: randomised controlled trial

Table 12: Cost per CRC case detected (£)as reported in Daniels (1995) using ministerial tariffs as the estimates of cost[114]

	Age	HO	Okokit
Sensitivity 55%	30-34	Not reported	82,461
	35-39	Not reported	25,119
	40-44	Not reported	14,843
	45-49	Not reported	6557
	50-54	Not reported	33,734
	55-59	Not reported	20,667
	60-64	Not reported	128,556
Sensitivity 55% Prevalence 5%	Screening started aged 40	16,411	15,881
Sensitivity 90% Prevalence 5%	Screening started aged 40	Not reported	9704
Prevalence 1.5%	Screening started aged 40	Not reported	5049

Table 13: Cost of screening for each subject with cancer (US $, converted from Italian Lira in 1996) as reported in Castiglione (1997) using ministerial tariffs as the estimates of cost[117]

	Age	HO	Immudia HemSp	
			Positive results only	Positive and borderline results
CRC	40 - 49	23,930	20,220	14,700
	50 - 70	12,900	9,020	10,000
Adenomas	40 - 49	7,990	12,130	7,350
	50 - 70	2,200	2,180	1,780
Adenomas >9mm	40 - 49	35,980	20,220	14,700
	50 - 70	4,530	3,860	3,730

Table 14: Cost per neoplasm detected as reported in Walker (1992)[115]

Strategy	Sensitivity	Specificity	Test cost (£)	Positives	Cancers detected	Total cost (£million)	Cost per cancer detected
HO: 3 day, no rehydration, no retesting	0.67	0.97	1.70	1 978	135	£0.38	£2,814
HO: all first round +ves retested	0.58	0.99	1.80	752	118	£0.26	£2,202
HO: all first round screenees retested	0.65	0.99	1.85	880	131	£0.28	£2,116
HO: rehydrated, no retesting	0.72	0.95	1.80	3 025	145	£0.50	£3,456
HO: 6 day, no rehydration, no retesting	0.74	0.99	3.40	882	137	£0.43	£3,156
Immudia HemSp	0.95	0.93	6.00	4 051	192	£1.03	£5,356
Feca-EIA	0.67	0.91	3.00	5 319	136	£0.86	£6,373
Coloscreen	0.33	0.94	1.00	5 327	99	£0.66	£6,691
EZ-detect	0.36	0.89	1.00	9 495	112	£1.11	£9,869

Table 15: Costs for unnamed guaiac and immunochemical FOBTs followed by colonoscopy, as reported in Shimbo (1994)[119]

	Guaiac	Immunochemcial
Cost per person (Yen)	72,660	49,850
Cost compared to no screening (Yen)	51,230	28,420
Incremental cost-effectiveness per year of life saved (Yen)	3,850,000	1,765,000
Incremental cost-effectiveness per year of life saved ($)	28,500	13,100

Table 16: Number of life years saved and costs (in Euros) for Haemoccult and Magstream as 10 and 20 year programmes as reported in Berchi (2004)[118]

	Number of life years saved	
	Haemoccult	**Magstream**
10 year programme	9.8	9.8
20 year programme	16.7	16.7
	Discounted cost of screening per person	
10 year programme	195	151
20 year programme	179	238
	Discounted incremental cost per life year saved Magstream (sensitivity 82%, specificity 96%) over HO (sensitivity 52%, specificity 99.5%)	
10 year programme	4141	
20 year programme	2980	

Table 17: Cost and ratio per per life year saved for an unnamed guaiac and immunochemical FOBT as reported in Wong (2004).[120]

	Incremental cost per life year saved compared with no screening (Singapore $)	
Age	**Guaiac**	**Immunochemical**
50-54	288.33	623.12
55-59	145.70	342.75
60-64	65.42	177.69
65-69	18.89	62.03
	Weighted incremental cost effectiveness ratio per life year saved compared with no screening	
	Guaiac	**Immunochemical**
	162.11	368.06

Guaiac: Sensitivity 10% polyps, 60% CRC, and specificity 90% polyps and CRC. Immunochemical: Sensitivity 40% polyps, 90% CRC and specificity 95% polyps and CRC.

Table 18: Cost per life year gained (LYG) in US $ for Haemoccult II (HO II), Haemoccult Sensa (HO Sensa), and an unnamed immunochemical FOBT (iFOBT) as reported in van Ballegooijen (2003)[116]

	Sensitivity (%)	**Specificity (%)**	**Test cost ($)**	**Surveillance**	**Average cost per LYG**
HO II	40	98	4.50	None	$1,071
HO Sensa	70	92.5			$3,342
iFOBT		98			$357
iFOBT		95			$1,994
HO Sensa		92.5	28		$5,827
iFOBT		98			$2,834
iFOBT		95			$4,479
HO II	40	98	4.50	Surveillance every 3 years	$2,245
iFOBT	70				$1,830
iFOBT			28		$4,161
iFOBT		95	4.50		$3,378
iFOBT			28		$5,716

5. DISCUSSION

With over 30,000 new cases of CRC being diagnosed each year in England and Wales (www.statistics.gov.uk), CRC represents a significant health problem and a potential target for screening. Screening for CRC using FOBTs has been shown in clinical trials to reduce mortality by 15 to 33% for average risk populations.[20-23] The feasibility of screening for CRC in the UK population using an FOBT was therefore investigated. Two pilot studies, one conducted in central England and the other in Scotland,[18, 26, 27] suggested that population based screening, using a guaiac based FOBT, is feasible, and that a national programme of FOBT screening should reduce mortality from CRC. However, the need for repeat-testing of 'weak positive' results lengthened the screening process. Further research to establish whether an immunochemical FOBT may provide more definitive results on the first test was recommended.[26] This review therefore evaluated the diagnostic accuracy and cost-effectiveness of both guaiac and immunochemical FOBTs, in an attempt to inform this debate.

5.1 Review methodology

Extensive literature searches were conducted in an attempt to identify maximum possible number of relevant studies. A broad spectrum of sources was considered particularly important for this review due to the high proportion of non-English language studies that were expected following scoping searches. Priority was given to maximising the sensitivity of the search strategies as search filters aimed at specifically identifying diagnostic accuracy studies are known to perform poorly.[123-127] Attempts were also made to identify unpublished research; these included contacting experts in the field and searching research registers, conference proceedings, grey literature, bibliographic references and the Internet, with a view to minimising the potential for publication bias. The extent to which publication bias is an issue for diagnostic accuracy studies remains unclear, and no validated method of assessing publication bias in diagnostic accuracy studies is currently available.[53] Intervention studies have a clear cut-off defining a 'positive result', i.e. whether there is a significant difference in outcome between the treatment and control, and whether this difference favours the intervention. This is not the case for diagnostic accuracy studies which measure the agreement between the results of the index test and a reference standard. It is likely that studies reporting higher estimates of test performance are published more frequently, but the extent to which this occurs is unclear. There is evidence that publication bias is a particular problem for studies of small sample size, although these data are not specific to the diagnostic literature.[128-130] The sample size of studies included in this review ranged from 44 to 97,205, with 24 diagnostic accuracy studies having fewer than 500 participants, and only ten having fewer than 200 participants; it may therefore be hypothesised that there is a reduced likelihood of significant impact from publication bias in this review.

During the initial study selection phase, we realised that many studies evaluating the effectiveness of a particular FOBT or the screening process in reducing mortality, which had not been designed to evaluate the diagnostic accuracy of FOBTs, contained useful information. By taking only data derived from the intervention arms (i.e. screened participants), these studies could be used to derive diagnostic cohorts that could then be included in the review. To increase the reliability of this data, we included only those derived cohorts with a loss to follow-up of less than 15%, and where all participants had received a reference standard or were followed up for at least two years. The generation of cohorts from these studies allowed us to make maximum use of the available data.

Clear inclusion criteria were reported in the protocol for this review, and a list of the studies that were assessed and excluded, along with the reason for their exclusion, is provided. All included studies were assessed for methodological quality using the QUADAS tool, which was developed specifically for the assessment of diagnostic accuracy studies.[131] The poor reporting of studies, an ongoing problem in diagnostics,[50] may limit the uefulness of this assessment, as it cannot always be ascertained whether a study that does not fulfil the QUADAS criteria is truly methodologically flawed, or just poorly reported.[132]

Established methods were used during the review process to reduce the potential for reviewer error or bias.[11] The initial stage of study selection (scanning titles and abstracts for relevance) was conducted independently by two reviewrs. The assessment of full papers for inclusion was conducted by one reviewer, with all potentially included studies and a random selection of potentially excluded studies checked by a second. Data extraction was carried out by one reviewer and checked by a second. All

disagreements were resolved by consensus or by referral to a third reviewer if consensus could not be reached.

5.2 Key findings of the review

A variety of FOBTs have been marketed for use in screening for CRC, including guaiac, immunochemical, haem-porphyrin and flushable FOBTs. The requirement of fluorescent spectrophotometry and complex laboratory procedures for haem-porphyrin, and the absence of a health professional in the interpretation of the results of flushable FOBTs, means these tests are not suitable as screening tools, and were not evaluated in this review.[18, 30, 31] Stool markers, such as detection of mutated DNA, tests for albumin, and calprotectin, were also not evaluated as these are still in the early phases of research.[12]

Currently, a range of FOBTs are used in screening programmes internationally, although the use of guaiac tests seem to predominate in Europe and the USA (primarily Haemoccult), and immunochemical tests in Asia. Where guaiac FOBTs have been evaluated in studies based in Asian countries, Shionogi B seems to be the most regularly used. The widespread use of Haemoccult in Europe and the USA has resulted in this FOBT being more extensively researched, with publications primarily in English and either of a diagnostic cohort design, or a study design from which a cohort could be derived. Of the 35 studies evaluating immunochemical FOBTs, 34 were conducted in Asia, of which 10 were published in Japanese or Chinese, with data extraction being undertaken via translators. In addition, the majority of studies conducted in Asia were of diagnostic case-control design (51% of studies of immunochemical FOBTs). Diagnostic case-control studies are more prone to bias and the over-estimation of accuracy.[132, 133] This was evident in the data included in the current review, as diagnostic case-control studies generally reported higher sensitivities for FOBTs than cohort studies. The results reported for immunochemcial FOBTs may therefore be less reliable, and more prone to data extraction errors (arising from translation) and bias (arising from methodological flaws in the primary studies), than those for guaiac FOBTs. As a result, any seemingly greater accuracy of immunochemical FOBT over guaiac FOBTs may be a consequence of the bias associated with the study design, rather than a clinically significant difference between the different test methodologies.

5.2.1 Guaiac FOBTs

Haemoccult and Haemoccult II differ only in their configuration, therefore these two tests were treated as one in the review.[110, 134] No one guaiac FOBT stood out as being better than the others. Data from diagnostic cohort studies indicated that KryptoHaem had the highest sensitivity for detecting all neoplasms, and non-rehydrated Haemoccult and Haemoccult Sensa had the highest sensitivity for detecting CRC. However, there were significant methodological flaws in these studies that require consideration. The only study to evaluate KryptoHaem[68] did not make it clear whether an appropriate patient spectrum had been recruited, and used sigmoidoscopy as the reference standard. Sigmoidoscopy does not examine the entire bowel, only identifying CRC in the distal bowel, therefore is not regarded an appropriate reference standard for the target condition. FOBTs tend to be better at detecting lesions in the distal bowel. This is more of an issue with immunochemical FOBTs than guaiac FOBTs, as immunochemical FOBTs rely on the detection of intact globin, which may have been degraded and become undetectable when bleeding originated from a lesion in the proximal bowel. Studies that use sigmoidoscopy as the reference standard may report an increased accuracy of the FOBT compared to those that use colonoscopy, as many of the additional lesions detected in the proximal bowel during colonoscopy, would not have been detected by the FOBT. The study reporting the highest sensitivity for Haemoccult Sensa for the detection of CRC[8] was of better quality, recruiting an appropriate patient spectrum (unselected screening population), and using colonoscopy as the reference standard after a positive FOBT. However the reference standard for people with a negative FOBT was referral to a cancer registry and follow-up, which would be likely to miss interval cancers. This may result in an under-estimation of the number of false negative results and hence an over-estimation sensitivity. Both studies reporting high sensitivities for Haemoccult (96.2%[106] and 86.8%[100] for the detection of CRC) used reference standards that were unlikely to adequately confirm the presence of disease after a positive FOBT result, or its absence after a negative result. One of the studies also did not make it clear whether an appropriate patient spectrum was used.[106] These methodological flaws in (or poor reporting of) the primary studies, make the reliability of reported results less certain,. The two highest quality cohort studies, one evaluating unrehydrated Haemoccult[80] and the other rehydrated Haemoccult[97] both recruited an appropriate patient spectrum

and used colonoscopy as the reference standard after both a positive and negative FOBT, reported low sensitivities for the detection of all neoplasms (19.3%[80] and 11.3%[97]) and much lower sensitivities for the detection of CRC (30.0%[80] and 34.1%[97]) than the lower quality studies.

The clinical and statistical heterogeneity seen between studies evaluating each guaiac FOBTs made pooling of study results inappropriate, and therefore no overall estimate of the accuracy of any guaiac FOBT could be calculated, limiting the value of the currently available data.

The effect of bias arising from inferior study designs can be clearly seen in the guaiac FOBT studies, as Haemoccult was generally reported as being more sensitive in the case-control studies than the cohort studies. Hence, although Shionogi B was reported as one of the most sensitive guaiac FOBTs, the fact that it was only evaluated in two case-control studies makes the reliability of these results uncertain.

There was little evidence to evaluate the benefit of repeat sampling. Only one small diagnostic case control study compared the accuracy of testing using Haemoccult for 1, 2 or 3 days,[6] and reported increases in sensitivity, and decreases in specificity with each additional day a test was completed.

5.2.2 Immunochemcial FOBTs

As immunochemical FOBTs use antibodies to detect the globin moiety of human haemoglobin, they are not only unaffected by diet, but they also will not detect bleeding from the upper GI tract as globin is degraded prior to entry into the colon.[45] This, along with the more convenient method of stool collection, has led to an increasing interest in and volume of research on the accuracy of immunochemical FOBTs and their usefulness for population screening. Immunochemcial FOBTs that utilised the same methodology (enzyme immunoassay, latex agglutination, reverse passive haemagglutination) were grouped together in this review. Data derived from the diagnostic cohort studies indicated that Immudia HemSp was the most sensitive immunochemical FOBT for the detection of all neoplasms. This test also performed fairly well, and more consistently than any other imunochemcial FOBT, for the detection of CRC. Although Flexsure, MonoHaem and OC Light had studies reporting sensitivities higher than Immudia HemSp for the detection of CRC, data were much less consistent between studies. In addition, the cohort study evaluating Immudia HemSp only failed to fulfil one QUADAS criterion; it did not describe the execution of the reference standard in sufficient detail to allow replication.[73] The other cohort studies either did not make it clear if an appropriate patient spectrum was recruited,[46] did not use an appropriate reference standard for people with a negative FOBT,[108] or the reference standard used was unclear,[46] or they did not provide sufficient details regarding the index test to allow replication.[71, 96, 108] The diagnostic case-control studies also reported favourable results for Immudia HemSp, with this test achieving the three highest reported sensitivities for the detection of all neoplasms. The variation in accuracy between tests was less pronounced than in the cohort studies.

The clinical and statistical heterogeneity seen between studies evaluating each immunochemcial FOBT made pooling of study results inappropriate, and therefore no overall estimate of the accuracy of any immunochemcial FOBTs could be calculated, limiting the value of the currently available data.

There was little evidence to evaluate the benefit of repeat sampling. The same small diagnostic case control study that evaluated the accuracy of Haemoccult with repeat testing, also compared Feca-EIA and OC Light when used for 1, 2 or 3 days.[6] As with Haemoccult, this study reported increases in sensitivity, and decreases in specificity with each additional day a test was completed.

5.3 Variability and limitations of the included studies

There are a number of potential sources of heterogeneity between the studies. The most obvious include study design, patient spectrum, reference standards used, the threshold used to define a positive result, as well as test specific details (e.g. rehydration and dietary restrictions for guaiac FOBTs). Though the available data were not sufficient to permit a full investigation of the impact of potential sources of heterogeneity on estimates of diagnostic accuracy using regression analyses, some of the possible effects are outlined and discussed below.

Study design
Only diagnostic cohort studies (some of which were derived from studies of other designs) and diagnostic case-control studies were located and included in the review. Many of the cohort studies were methodologically flawed, particularly in relation to the patient spectrum and the reference standards used. Case-control studies are known to be more prone to bias and have a tendency to produce overestimations of diagnostic accuracy.[132, 133] Data included in the current review support this, in particular, case-control studies evaluating Haemoccult tended to report greater sensitivity than cohort studies. As most studies evaluating immunochemical FOBTs were case-control studies, these data need to be treated with particular caution, and the consequent additional difficulties in comparing guiac and immunochemical FOBTs noted.

Furthermore, there was a lack of studies that made direct comparisons between guaiac and immunochemical FOBTs. Only direct comparisons, where both guaiac and immunochemcial FOBTs are used to test the same stool specimens, will provide the data needed to compare the accuracy of these two types of FOBT.

The standard of reporting in the primary studies was a problem throughout the review. This issue has been highlighted previously.[47, 50, 63, 131, 135, 136] The Standards for Reporting of Diagnostic Accuracy (STARD) group published a checklist to improve the quality of reporting of a diagnostic studies,[63, 135, 136] and some evidence of improved reporting quality has been noted in the general diagnostic literature.[135, 136] Quality and consistency of reporting remains an area of concern for primary diagnostic accuracy studies, which is likely to limit the utility of evidence synthesis in this area.

Reference standards
Colonoscopy to the caecum is likely to be the most accurate diagnostic tool for the detection of colorectal neoplasms, and was regarded as the gold standard in this review. Positive FOBT/cases often received colonoscopy or a combination of tests that were likely to diagnose target condition. However, many of the reference standards used, particularly for those with negative FOBT/controls, such as sigmoidoscopy, or referral to the cancer registry, had limitations, and would not necessarily identify the target condition. The use of reference standards that may not identify the target condition in those with a negative FOBT could result in an underestimation of the number of false negatives and hence an over estimation of sensitivity.

Thresholds
Changing the threshold for positivity (e.g. the number of windows required to show blue colouration on a Haemoccult slide) may change both the sensitivity and specificity of the test. Some studies stated that 'any blue colour' indicated a positive result, others specified that 2, 3 or more windows had to show a blue colouration to be positive, and some studies retested after what were considered 'weak' positive results. These differences in threshold will affect the observed positivity rate of the test, and as such, will impact on the proposed number of colonoscopies that would be required as a result of a screening programme with FOBT.

Hydration
The hydration status of the faecal sample is only an issue for guaiac FOBTs, and is primarily seen as an issue for Haemoccult slides. Hydration of Haemoccult slides before development and interpretation of the results is thought to impact on the accuracy of the test, with an increase in sensitivity with rehydration.[137, 138] Only an indirect comparison of results from cohort studies was available to investigate this potential source of heterogeneity, as no study provided a direct comparison of rehydrated and non-rehydrated Haemoccult slides. Indirrect comparison of data reported in this review provided no evidence that rehydration increased the sensitivity of Haemoccult. In fact, the lowest reported sensitivities were similar, both for all neoplasms and for CRC, with the highest reported sensitivities being for non-rehydrated Haemoccult slides. Overall specificity was comparable between rehydrated and non-rehydrated Haemoccult slides, although studies that did not rehydrate the slides reported a wider range of specificities than those that did. The limited regression analysis that was possible indicated that rehydration had no affect on overall accuracy (as indicated by DOR).

Diet and medication use
Another factor that may explain some of the heterogeneity between studies evaluating guaiac FOBTs is the use (or not) of restrictions to diet and medication. As guaiac FOBTs depend upon the detection of peroxidase or pseudo-peroxidase activity, and are not specific to the pseudoperoxidase activity of

human haemoglobin, diet and medications are thought to influence the accuracy of the test.[138] For example animal haemoglobin/myoglobin in red meat may increase the number of false positive results, as may fruits and vegetables high in peroxidase activity (artichokes, bananas, turnips, horseradish, mushrooms, radishes, broccoli, bean sprouts, cauliflower, oranges, grapes), the use of aspirin, nonsteroidal anti-inflammatory drugs, and other gastric irritants that may cause bleeding.[138] The antioxidant, ascorbic acid, interferes with the pseudoperoxidase reaction, therefore high doses of vitamin C may increase the number of false negative results.[139] Only the group of studies evaluating Haemoccult for the detection of CRC included studies of the same design that did,[8, 64, 65, 67, 94, 97, 100, 106, 110, 113] and did not,[69, 80] impose dietary restrictions prior to testing. Indirect comparison of this limited data found no indication that imposing dietary restriction improved the accuracy of Haemoccult for the detection of CRC. The limited regression analysis that was possible indicated that dietary restriction had no affect on overall accuracy (as indicated by DOR).

Dietary restrictions imposed prior to testing with guaiac FOBTs are also thought to be a factor in reducing compliance.[43, 140] However, results from a published review suggested that advice to apply modest dietary restriction when using non-rehydrated FOBTs did not affect the completion rate, although more severe restrictions may.[37]This review also reported that dietary restriction did not appear to affect positivity rates and concluded that dietary restrictions should not be imposed before testing with non-rehydrated FOBTs.[37] There was insufficient data regarding the impact of dietary restrictions on compliance in the included studies to draw any conclusions.

5.4 Economic evaluations

Cost-effectiveness evaluations used higher values of sensitivity and lower values of specificity than those presented in this review. Therefore the hypothetical scenarios described in these economic evaluations have limited value. The choice of the comparators appears to have been appropriate in most studies, however the methods used to find and select the primary studies were unclear, and several assumptions about the appropriateness of the benefit measures had to be made. None of the studies assessed the impact of FOBTs on quality of life. The unit costs were provided in all studies. However, the issue of the generalisability of the study results to other settings was partially addressed in only one study.[114] Currently, published evidence about the relative specificity and sensitivity of immunochemical FOBTs in comparison to guaiac FOBTs is sparse and highly uncertain, limiting the possibilities for cost-effectiveness evaluations. Our findings support the claim that more cost-effectiveness evaluations in clinical settings should be performed,[124] with the caveate that reliable comparative accuracy data are required to inform economic modelling.

5.5 Guaiac or immunochemical FOB testing?

Studies performing direct comparisons between guaiac and immunochemical FOBTs, (i.e. performing more than one test on the same stool specimen) gave inconsistent and often conflicting results. With few studies reporting results for direct comparisons between FOBTs, the review also attempted indirect comparisons between guaiac and immunochemical FOBTs.

There was some support for one immunochemical FOBT (Immudia HemSp) being superior to other immunochemical FOBTs evaluated. However, there was little support for the superiority of any one guaiac FOBT. There was also no clear evidence to suggest that either guaiac or immunochemical FOBTs performed better than the other, either for the detection of all neoplasms or CRC. The test reported to be most sensitive in the diagnostic cohort studies for the detection of all neoplasms was the guaiac FOBT KryptoHaem,[68] with the immunochecmial FOBT, Immudia HemSp, being second.[73] The quality of the studies evaluating Immudia HemSp, however, was generally good, whereas the single study evaluating KryptoHaem had significant methodological flaws. The data on Immudia HemSp may therefore be a more reliable reflection of the test's performance. For the detection of CRC, data form cohort studies indicated that Haemoccult and MonoHaem were likely to be the most sensitive tests evaluated. However, there was a large variation in the sensitivities of both guaiac and immunochemical FOBTs, with no FOBT being consistently more sensitive than the others.

Overall, therefore, Immudia HemSp seems to be the most reliable test (based on currently available data) for the detection of all neoplasms, which would be the main aim for any programme screening in an asypmtomatic population. The cost effectiveness of Immudia HemSp was evaluated in two economic evaluations, one conducted in the UK[115] and the other in Italy.[117] Both studies used

Haemoccult as the comparator guaiac FOBT. The study conducted in the UK reported that Immudia HemSp was less cost-effective (cost per cancer detected) than Haemoccult. The Italian study, however, reported that Immudia HemSp was the more cost effective (cost of screening each person with cancer) option for the detection of CRC, and adenomas, when both definite positives and borderline positive results were taken into consideration, in both the 40-49 and 50-70 year age groups.[117] Further research is required in this area.

A recent report, published by the Blue Cross and Blue Shield Association,[45] reviewed seven studies performed in high risk populations, that compared guaiac and immunochemical FOBTs. This report concluded that there was not enough evidence for applying immunochemical FOBTs on a larger scale, and that the scientific evidence should improve.[45] Whilst reporting tentative data in support of Immudia HemSp, our findings generally support this view.

In choosing an FOBT for use in a national screening programme, the likely number of colonoscopies that would be carried out as a consequence of the differing positivity rates of tests is an important practical consideration. Given that the limit of detection for haemoglobin in stool samples is lower for immunochemical FOBTs than for guaiac FOBTs,[141-143] it may be expected that more colonosocpies would need to be conducted when using an immunochemical FOBTs than guaiac. However, the applicability of the estimates of the limit of detection calculated using *in vitro* studies to the level of blood loss from a neoplasm is uncertain. Using data derived from diagnostic cohort studies included in this review, (FOBT for the detection of all neoplasms,) it is possible to estimate the number of colonoscopies that would be undertaken for every 1000 people screened (if 80% of those with a positive FOBT agreed to a colonoscopy), as well as how many of these would have been conducted after false positive tests, and were therefore unnecessary.

From the limited data availble, the estimated number of colonoscopies that would be conducted per 1000 people screened using un-rehydrated Haemoccult (the FOBT used in the UK screening pilot) would be between 11 (7 conducted after false positive results) and 160 (114 after false positive results).[64, 65, 67, 77, 78, 80, 113] The estimated number of colonoscopies, derived from the single study of , KryptoHaem (a study which, though flawed, also reported the highest diagnostic accuracy) would be 29 (12 after false positive results).[68] The number of colonoscopies that would be required after immunochemical FOBTs, ranged from 18 (9 after false positive results) for OC Light[71] to 90 (83 after false positive results) for the SPA Test,[46] with the positivity rate reported in the study evaluating Immudia HemSp resulting in a need for 63 colonoscopies (44 after false positive results).[73]

These estimates indicate that, regardless of the FOBT used, a large number of colonoscopies would be likely to be conducted after false positive results. Such a scenario would impact upon the infrastructure requirements and cost of a screening programme, and would be likely to result in significant numbers of people experiencing unnecessary stress, anxiety and physical discomfort. They also indicate that the lower limit of detection for haemoglobin seen in *in vitro* studies of immunochemical FOBTs does not translate to an increase in the number of potential colonoscopies when the test is used in a screening context.

Using census data to calculate the number of people who would be eligbile for screening, we can estimate the total number of colonoscopies that may be required for a screening population. If screening was offered to people aged between 60 and 69 (5,600,000 people), and 60% (3,360,000 people) accepted screening,[144] between 36,960 and 538,000 colonoscopies would need to be conducted based on the lowest and highest positivity rates (both of which were for un-rehydrated Haemoccult) reported for the tests evaluated evaluated in this review. As is clear from the wide range in possible extimates of the number of colonoscopies arising from a UK screening programe, no firm conclusions can be drawn from the data presented in this review regarding either the number of colonoscopies that would need to be conducted if a given screening test were adopted, how many of these would be conducted unnecessarily, or what would be the health and economic costs of “false” screening results. Further, research is much needed in this area.

6. CONCLUSIONS

Studies that included direct comparisons indicated a better overall test performance for immunochemical FOBTs than for guaiac FOBTs, but this evidence was very limited and of poor quality. Indirect comparisons showed no clear evidence to suggest that either guaiac or immunochemical FOBTs performed better. Poor reporting of data limited the scope of this review. We would encourage investigators to use the STARD guidelines when reporting diagnostic accuracy studies.

6.1 Implications for practice

Of the guaiac FOBTs, KryptoHaem appeared to show the best overall accuracy for the detection of all neoplasms. However, KryptoHaem was only evaluated in a single cohort study, which had significant methodological flaws. On the whole, Haemoccult Sensa appeared to be more sensitive than Haemoccult, with similar specificity. Amongst the immunochemical FOBTs, Immudia HemSp appeared to perform best for the detection of all neoplasms, and, athough MonoHaem and Iatro HemCheck appeared more accurate for the detection of CRC, Immudia HemSp produced the most consistent results across studies. Sensitivity was generally increased for all tests where CRC was the target condition rather than all neoplasms.

The few direct comparisons between guaiac and immunochemical FOBTs available, gave inconsistent and often conflicting results. With few studies reporting results for direct comparisons between FOBTs, the review also attempted indirect comparisons between guaiac and immunochemical FOBTs. Less reliable indirect comparisons showed no clear preference for either guaiac or immunochemical FOBTs. However, sensitivities derived from cohort studies were generally low, with the sensitivity being less than 50% in 89% of studies for the detection of all neoplasmsm and 50% of studies for the detection of CRC. The 'miss rate' at a single screening is therefore likely to be high regardless of the FOBT used.

When deciding on which FOBTs to use as a screening tool for colorectal neoplasms, the following points should be considered:

- Overall test accuracy*:* the number of false positive and false negative results generated by an FOBT will impact on the number of colonoscopies performed, patient attitudes, physchiatric morbididty, compliance, and cost-effectiveness. Though comparative data are sparse, it seems that some immunochemical tests, particularly Immudia HemSp, may be more consistent in their level of accuracy than other FOBTs.
- Compliance*:* this may vary considerably with different collection techniques, need for dietary restrictions with some tests, and the frequency of testing required. In this regard, it seems likely that compliance would be greater with immunochemical tests than guaiac FOBTs, as the collection method is easier, with less contact with the stool specimen, and dietary restrictions are not required. However, there is little evidence to support this hypothesis.
- Practical elements, such as posting the tests: concerns have been raised about the ability of post offices to handle immunochemical FOBTs, this might have important implications when adopting such tests.
- Cost-effectiveness: on the whole, it seems that immunochemical FOBTs may be more costly, however, the impact of this may be offset if improvements in accuracy and compliance are demonstrated.
- Availability in the UK.

6.2 Implications for research

Based on the current evidence, further research is required to fully evaluate the comparative diagnostic accuracy of FOBTs. Well designed diagnostic cohort studies are to be preferred over case control studies, and the following specific points should be considered when designing a study:

1. Population spectrum should be clearly defined *a priori*, and designed to measure the diagnostic accuracy of FOBTs in a population representative that targeted for screening. Ideally, multi-centre studies should be conducted with a view to providing a more representative sample of the general screening population. Inappropriate exclusion of participants after entering the study and exclusion of borderline or uninterpretable results should be avoided.
2. Studies should ideally use the same reference standard to confirm diagnosis, regardless of the result of the FOBT.
3. The detection of all neoplasms (cancer and adenomas) should be the main diagnostic target of any study, as this would be the aim of a national screening programme.
4. Those interpreting tests in a study setting should have access to similar, relevant clinical information to that which would be available in the context of a screening programme, and should be blinded to other information.
5. Direct comparisons between immunochemical FOBTs, and between guaiac and immunochemical FOBTs are required. Most of the research on immunochemical FOBTs has been conducted in Asian countries, using a case-control study design, therefore these data may not be generalisable to the UK setting, and may be prone to bias.

In addition, the regular provision of information regarding the outcomes of the NHS Bowel Cancer Screening Programme, particularly in realtion to the number of colonoscopies performed and associated beneficial/adverse outcomes, may greatly increase the evidence base.

Further areas where research is required include:

1. The impact of dietary restrictions and re-hydration on the accuracy of and compliance with guaiac FOBTs. Many researchers do not recommend the use of re-hydration, and there is still controversy over whether dietary restrictions should be applied, particularly for Haemoccult Sensa.
2. The number of colonoscopies that would be required in the UK screening population based on the positivity rates of different tests, and the impact upon the infrastructure requirements and cost of a screening programme.
3. The acceptability of different FOBTs to those being screened. For example brush versus spatula collection methods, the requirement of dietary restrictions for some tests, the need for repeat testing, and the frequency of testing required on acceptability and compliance.
4. The impact of both false positive and false negative results on psychiatric morbidity, future self referral with onset of symptoms, and attendance at rescreening sessions.
5. The skills and experience of those conducting and interpreting diagnostic tests may be a source of variation in diagnostic accuracy, particularly where interpretation is subjective. Although outside the scope of this review, both intra- and inter-user variability and the relationship of the latter to skills and experience, are of potential interest.

More complete reporting of data using the STARD recommendations when publishing research results is recommended.[135, 136] Details as to how the index tests and reference standard were performed should be made explicit to allow replication.

7. REFERENCES

1. Miyoshi H, Shimamoto C, Hirata I, Tsumoto S, Amatsu T, Oshiba S, et al. [The clinical study of the new immunological detection test (stick EIA) for faecal occult blood: first report]. *Prog Med* 1988;8:1510-12.

2. Matsuse R, Uchida K, Miyachi N, Okuda S, Tomita S, Miyoshi H, et al. [Immunochemical detection of fecal occult blood by latex-agglutination reaction for hemoglobin and transferrin]. *Latest Medical Science* 1989;44:2636-41.

3. Takeshita T, Sugimoto N, Ashizawa S. [Mass screening for colo-rectal cancer by fecal occult blood test]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1982;35:561-66.

4. Takeshita T, Horiguchi J, Kinoshita T, et al. [Immunological fecal occult blood testing with anti-human hemoglobin antibody]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1985;38:369-75.

5. Allison JE, Levin T, Sakoda L, Tucker J, Tekawa I, Pauly MP, et al. The new fecal occult blood tests have poor application sensitivity for significant polyps in average risk subjects. *Gastroenterology* 2002;122:A592-A93.

6. Kikkawa N, Takeuchi H, Kawahara T, Okamoto M, Funahashi S, Yamamoto A. [Comparison of chemical and immunological methods in fecal occult blood testing]. *Gan No Rinsho* 1987;33:1049-51.

7. Nakama H, Kamijo N. Accuracy of immunological fecal occult blood testing for colorectal cancer screening. *Prev Med* 1994;23:309-13.

8. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;334:155-9.

9. Miyoshi H, Ohshiba S, Asada S, Hirata I, Uchida K. Immunological determination of fecal hemoglobin and transferrin levels: a comparison with other fecal occult blood tests. *Am J Gastroenterol* 1992;87:67-73.

10. St.John DJ, Young GP, Alexeyeff MA, Deacon MC, Cuthbertson AM, Macrae FA, et al. Evaluation of new occult blood tests for detection of colorectal neoplasia. *Gastroenterology* 1993;104:1661-8.

11. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or comissioning reviews. CRD Report 4*. 2nd ed. York: NHS Centre for Reviews and Dissemination, 2001.

12. Strul H, Arber N. Fecal occult blood test for colorectal cancer screening. *Ann Oncol* 2002;13:51-6.

13. Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJL. *Cancer incidence, mortality and survival by site for 14 regions of the world*. Geneva: World Health Organization, 2001.

14. Cancer Research UK. *CancerStats. UK Bowel Cancer incidence statistics [homepage on the Internet]*. Cancer Research UK; 2006. [cited 2006 Jul 4]. Available from: http://info.cancerresearchuk.org/cancerstats/types/bowel/incidence/.

15. National Statistics. *Cancer statistics registrations: registrations of cancer diagnosed in 2003, England. Series MB1 no. 34*. London: The Stationery Office, 2005.

16. Office for National Statistics. *Cancer incidence and mortality in the United Kingdom 2001-03 [Excel spreadsheet on the Internet]*. Office for National Statistics; 2005. [cited 2006 Jul 4]. Available from: http://www.statistics.gov.uk/statbase/Product.asp?vlnk=14209.

17. Quinn M, Babb P, Brook A, Kirby L, Jones J. *Cancer trends in England and Wales, 1950-1999*. London: The Stationery Office, 2001.

18. National Screening Committee, Department of Health. *A summary of the colorectal cancer screening workshops and background papers*. In. Leeds: Department of Health; 1998. p. 1-63.

19. Bond JH. Fecal occult blood test screening for colorectal cancer. *Gastrointest Endosc Clin N Am* 2002;12:11-21.

20. Faivre J, Dancourt V, Lejeune C, Tazi MA, Lamour J, Gerard D, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004;126:1674-80.

21. Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review. *JAMA* 2003;289:1288-96.

22. Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale: update based on new evidence. *Gastroenterology* 2003;124:544-60.

23. Young GP, St John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. *Am J Gastroenterol* 2002;97:2499-507.

24. Bowles CJ, Leicester R, Romaya C, Swarbrick E, Williams CB, Epstein O. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? *Gut* 2004;53:277-83.

25. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. *BMJ* 1998;317:559-65.

26. The CRC Screening Pilot Evaluation Team. *Evaluation of the UK colorectal cancer screening pilot. Final report (February 2003, revised May 2003)*: NHS Cancer Screening Programmes; 2003. Available from: http://www.cancerscreening.nhs.uk/colorectal/finalreport.pdf

27. UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. *BMJ* 2004;329:133-35.

28. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.

29. Bond JH. Screening guidelines for colorectal cancer. *Am J Med* 1999;106:7S-10S.

30. Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med* 1999;341:38-46.

31. Pearson SM. MDA evaluation of 11 faecal occult blood test kits. In: Martin SM, editor. *Proceedings of Pathology*; 2000; Birmingham. London; IBMS; 2000. p. 114.

32. Selinger RR, Norman S, Dominitz JA. Failure of health care professionals to interpret fecal occult blood tests accurately. *Am J Med* 2003;114:64-7.

33. Ransohoff DF, Lang CA. Screening for colorectal cancer with the fecal occult blood test: a background paper American College of Physicians. *Ann Intern Med* 1997;126:811-22.

34. Ransohoff DF, Lang CA, Thibault GE, Feussner JR, Audet AM, Friesinger GC, Jr., et al. Suggested technique for fecal occult blood testing and interpretation in colorectal cancer screening. *Ann Intern Med* 1997;126:808-10.

35. Launoy GD, Bertrand HJ, Berchi C, Talbourdet VY, Guizard AV, Bouvier VM, et al. Evaluation of an immunochemical fecal occult blood test with automated reading in screening for colorectal cancer in a general average-risk population. *Int J Cancer* 2005;115:493-6.

36. Walsh JM, Terdiman JP. Colorectal cancer screening: clinical applications. *JAMA* 2003;289:1297-302.

37. Pignone M, Campbell MK, Carr C, Phillips C. Meta-analysis of dietary restriction during fecal occult blood testing. *Eff Clin Pract* 2001;4:150-6.

38. Allison JE. Review article: faecal occult blood testing for colorectal cancer. *Aliment Pharmacol Ther* 1998;12:1-10.

39. Fleisher M, Winawer SJ, Zauber AG, Smith C, Schwartz MK, and the National Polyp Study Work Group. Accuracy of fecal occult blood test interpretation. *Ann Intern Med* 1991;114:875-6.

40. Levin B, Brooks D, Smith RA, Stone A. Emerging technologies in screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. *CA Cancer J Clin* 2003;53:44-55.

41. Ransohoff DF, Pignone M. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2001;344:1022-3.

42. Nakama H, Fattah A, Zhang B, Uehara Y, Wang C. A comparative study of immunochemical fecal tests for detection of colorectal adenomatous polyps. *Hepatogastroenterology* 2000;47:386-9.

43. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen* 2003;10:117-22.

44. Castiglione G, Grazzini G, Miccinesi G, Rubeca T, Sani C, Turco P, et al. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. *J Med Screen* 2002;9:99-103.

45. Blue Cross, Blue Shield Association. *Immunochemical versus guaiac fecal occult blood tests*. Chicago: Blue Cross Blue Shield Association; 2004. Available from: http://www.bcbs.com/tec/vol19/19_05.html

46. Zhou DY, Feng FC, Zhang YL, Lai ZS, Zhang WD, Li LB, et al. Comparison of Shams' test for rectal mucus to an immunological test for fecal occult blood in large intestinal carcinoma screening: analysis of a check-up of 6480 asymptomatic subjects. *Chin Med J (Engl)* 1993;106:739-42.

47. Whiting P, Rutjes AW, Dinnes J, Reitsma J, Bossuyt PM, Kleijnen J. Development and validation of methods for assessing the quality of diagnostic accuracy studies. *Health Technol Assess* 2004;8:1-234.

48. Honest H, Bachmann LM, Khan K. Electronic searching of the literature for systematic reviews of screening and diagnostic tests for preterm birth. *Eur J Obstet Gynecol Reprod Biol* 2003;107:19-23.

49. Honest H, Khan KS. Reporting of measures of accuracy in systematic reviews of diagnostic literature. *BMC Health Serv Res* 2002;2:4.

50. Smidt N, Rutjes AW, van der Windt DA, Ostelo RW, Reitsma JB, Bossuyt PM, et al. Quality of reporting of diagnostic accuracy studies. *Radiology* 2005;235:347-53.

51. Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. *Ann Intern Med* 2004;140:189-202.

52. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. *Stat Med* 2002;21:1525-37.

53. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ* 2001;323:157-62.

54. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW. Critical assessment of economic evaluation. In: *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford: Oxford University Press; 1997. p. 27-51.

55. *FDA-registered medical devices. Medical speciality: hematology. Classification: reagent, occult blood [homepage on the Internet]*. Zapconnect.com Medical Devices Industry Portal; [cited 2005 Mar 21]. Available from: http://www.zapconnect.com/search/products/fda_approved/index.cfm/fuseaction/search_products_fda_approved_proprietary_device_name_list/medical_specialty_code/HE/medical_specialty/Hematology/product_code/KHE/classification_name/REAGENT,%20OCCULT%20BLOOD.

56. Zamora J, Muriel A, Abraira V. Meta-DiSc for Windows: a software package for the meta-analysis of diagnostic tests. In: *XI Cochrane Colloquium.*; 2003; Barcelona. 2003. Available from: http://www.hrc.es/investigacion/metadisc.html

57. Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. *Stat Med* 1993;12:1293-316.

58. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45.

59. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. *Stat Med* 1988;7:889-94.

60. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.

61. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

62. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

63. Bossuyt PM, Reitsma JB, Standards for Reporting of Diagnostic Accuracy. The STARD initiative. *Lancet* 2003;361:71.

64. Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value: long-term follow-up in a large group practice setting. *Ann Intern Med* 1990;112:328-33.

65. Bang KM, Tillett S, Hoar SK, Blair A, McDougall V. Sensitivity of fecal hemoccult testing and flexible sigmoidoscopy for colorectal cancer screening. *J Occup Med* 1986;28:709-13.

66. Chen HS, Sheen-Chen SM. Influence of age and gender on surveillance for colorectal tumors in low-risk asymptomatic population. *Anticancer Res* 2002;22:399-403.

67. Foley DP, Dunne P, Dervan PJ, Callaghan TWO, Crowe J, Lennon JR. Left-sided colonoscopy and hemoccult screening for colorectal neoplasia. *Eur J Gastroenterol Hepatol* 1992;4:925-36.

68. Klug W, Knoch HG. [What does the Krypto-Haem test accomplish in occult hemorrhage from the large intestine?]. *Z Arztl Fortbild (Jena)* 1983;77:516-9.

69. Launoy G, Smith TC, Duffy SW, Bouvier V. Colorectal cancer mass-screening: estimation of faecal occult blood test sensitivity, taking into account cancer mean sojourn time. *Int J Cancer* 1997;73:220-4.

70. Lieberman DA, Weiss DG, for the Veterans Affairs Cooperative Study Group 380. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001;345:555-60.

71. Liu HH, Huang TW, Chen HL, Wang TH, Lin JT. Clinicopathologic significance of immunohistochemical fecal occult blood test in subjects receiving bidirectional endoscopy. *Hepatogastroenterology* 2003;50:1390-2.

72. Murakami R, Otani T, Nakanishi K, Fudemoto Y, Ishikawa H, Hiyama T, et al. Diagnostic validity of fecal occult blood tests for detecting gastroenterological cancers. *Jpn J Cancer Res* 1992;83:141-5.

73. Nakama H, Zhang B, Fattah AA, Kamijo N, Zhang X. Characteristics of colorectal cancer that produce positive immunochemical occult blood test results on stool obtained by digital rectal examination. *Can J Gastroenterol* 2001;15:227-30.

74. Nakama H, Zhang B, Fattah AS, Zhang X. Colorectal cancer in iron deficiency anemia with a positive result on immunochemical fecal occult blood. *Int J Colorectal Dis* 2000;15:271-4.

75. Nakama H, Fattah AS, Zhang B, Kamijo N. Digital rectal examination sampling of stool is less predictive of significant colorectal pathology than stool passed spontaneously. *Eur J Gastroenterol Hepatol* 2000;12:1235-8.

76. Nakama H, Zhang B, Abdul Fattah AS, Kamijo N, Fukazawa K. Relationships between a sign of rectal bleeding and the results of an immunochemical occult blood test, and colorectal cancer. *Eur J Cancer Prev* 2000;9:325-8.

77. Parikh A, Ramamoorthy R, Kim KH, Holland BK, Houghton J. Fecal occult blood testing in a noncompliant inner city minority population: increased compliance and adherence to screening procedures without loss of test sensitivity using stool obtained at the time of in-office rectal examination. *Am J Gastroenterol* 2001;96:1908-13.

78. Ribet A, Frexinos J, Escourrou J, Delpu J. Occult blood tests and colorectal tumours. *Lancet* 1980;1:417.

79. St.John DJ, Young GP, McHutchison JG, Deacon MC, Alexeyeff MA. Comparison of the specificity and sensitivity of Hemoccult and HemoQuant in screening for colorectal neoplasia. *Ann Intern Med* 1992;117:376-82.

80. Sung JJ, Chan FK, Leung WK, Wu JC, Lau JY, Ching J, et al. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. *Gastroenterology* 2003;124:608-14.

81. Bhattacharya I, Sack EM. Screening colonoscopy is an effective as colonoscopy for a positive fecal occult blood test (FOBT) for the detection of colorectal neoplasia in average risk asymptomatic patients 60-75 years old. *Gastroenterology* 1997;112 (4 Suppl):A538.

82. Kawai K. Clinical study on MonoHaem, an immunological fecal occult blood test reagent. *Nippon Daicho Komonbyo Gakkai Zasshi* 1987;40:308-13.

83. Lampe J, Jacobasch KH, Uhlig K. Krypto-haem SSWR, ein testbrief zum nachweis von okkultem blut im stuhl. *Dtsch Gesundh Wes* 1982;37:175-77.

84. Li S, Zhang C, Xu E. [Evaluation of combined test of sequential fecal occult blood and albumin in the screening of colorectal neoplasms]. *Zhonghua Zhong Liu Za Zhi* 1995;17:381-3.

85. Nakama H, Zhang B, Kamijo N. Sensitivity of immunochemical fecal occult blood test for colorectal flat adenomas. *Hepatogastroenterology* 2004;51:1333-36.

86. Nakama H, Abdul Fattah AS, Zhang B, Kamijo N, Fujimori K, Miyata K. Detection rate of immunochemical fecal occult blood test for colorectal adenomatous polyps with severe dysplasia. *J Gastroenterol* 1997;32:492-5.

87. Nakama H, Kamijo N, Fujimori K, Fattah AS, Zhang B. Diagnostic accuracy of immunochemical faecal occult blood test for gastric cancer. *J Med Screen* 1996;3:113-4.

88. Tada M, Hosokawa N, Shimizu S, et al. Evaluation of a new fecal occult blood test. *J Kyoto Prefectural University of Medicine* 1986;95:1331-7.

89. Tada M. [New immunological fecal occult blood test applying latex inhibition method]. *Medical Science and Pharmaceuticals* 1988;20:1271-77.

90. Zhang B, Nakama H, Fattah AS, Kamijo N. Lower specificity of occult-blood test on stool collected by digital rectal examination. *Hepatogastroenterology* 2002;49:165-7.

91. Zhou PH, Zhang WZ. Experimental study on reverse passive hemagglutination for detection of human fecal occult blood. *Natl Med J China* 1987;67:671-72.

92. Zhu WX, Lin JJ. Reverse passive hemagglutination for detection of fecal occult blood: a comparison with Japanese Immudia-Hem SP Kit. *Chin Med J (Engl)* 1988;101:519-22.

93. Bennett DH, Hardcastle JD, Moshakis V, Rubin R, Berry D, Vellacott K, et al. A comparison of screening for colorectal cancer by flexible sigmoidoscopy and faecal occult blood testing (FOBT) with FOBT alone. *Gastroenterology* 1996;110:A491.

94. Castiglione G, Grazzini G, Poli A, Bonardi R, Ciatto S. Hemoccult sensitivity estimate in a screening program for colorectal cancer in the Province of Florence. *Tumori* 1991;77:243-5.

95. Chen K, Jiao DA, Zheng S, Zhou L, Yu H, Yuan YC, et al. Diagnostic value of fecal occult blood testing for screening colorectal cancer. *China Natl J New Gastroenterol* 1997;3:166-68.

96. Cheng TI, Wong JM, Hong CF, Cheng SH, Cheng TJ, Shieh MJ, et al. Colorectal cancer screening in asymptomaic adults: comparison of colonoscopy, sigmoidoscopy and fecal occult blood tests. *J Formos Med Assoc* 2002;101:685-90.

97. Collins JF, Lieberman DA, Durbin TE, Weiss DG, and the Veterans Affairs Cooperative Study #380 Group. Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. *Ann Intern Med* 2005;142:81-85.

98. Itoh M, Takahashi K, Nishida H, Sakagami K, Okubo T. Estimation of the optimal cut off point in a new immunological faecal occult blood test in a corporate colorectal cancer screening programme. *J Med Screen* 1996;3:66-71.

99. Kim YH, Kim J, Son HJ, Rhee PL, Koh KC, Paik SW, et al. Immunochemical fecal occult blood test for detection of rectosigmoid cancer in asymptomatic adults. *Gastroenterology* 1998;114:A625.

100. Michalek AM, Cummings KM, Gamble D. The use of a cancer registry in a mass screening program for colorectal cancer. *Cancer Detect Prev* 1988;11:353-7.

101. Morikawa T, Kato J, Yamaji Y, Wada R, Kokubo T, Mitsushima T, et al. Pitfall of immunological fecal occult blood test: a comparison with total colonoscopy. *Gastrointest Endosc* 2004;59:AB286.

102. Nakama H, Kamijo N, Abdul Fattah AS, Zhang B. Validity of immunological faecal occult blood screening for colorectal cancer: a follow up study. *J Med Screen* 1996;3:63-5.

103. Okamoto M, Kawabe T, Shiratori Y, Omata M, Maeda Y, Yamaji H, et al. Risk for colorectal cancer in patients with positive fecal occult blood test: analysis on 5648 asymptomatic patients performed total colonoscopy. *Gastroenterology* 1997;112:A632.

104. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. *J Med Screen* 2002;9:7-10.

105. Rennert G, Rennert HS, Miron E, Peterburg Y. Population colorectal cancer screening with fecal occult blood test. *Cancer Epidemiol Biomarkers Prev* 2001;10:1165-8.

106. Winawer SJ, Schottenfeld D, Miller D, Sherlock P, Deschner E, Stearns M, et al. Detection of early colon cancer and colonic polyps. In: Nieburgs HE, editor. *Prevention and detection of cancer: Proceedings of the Third International Symposium on Detection and Prevention of Cancer, New York 1976, Part II, Vol. 2*. New York: Marcel Dekker; 1980. p. 2103-10.

107. Brevinge H, Lindholm E, Buntzen S, Kewenter J. Screening for colorectal neoplasia with faecal occult blood testing compared with flexible sigmoidoscopy directly in a 55-56 years' old population. *Int J Colorectal Dis* 1997;12:291-5.

108. Gondal G, Grotmol T, Hofstad B, Bretthauer M, Eide TJ, Hoff G. The Norwegian Colorectal Cancer Prevention (NORCCAP) screening study: baseline findings and implementations for clinical work-up in age groups 50-64 years. *Scand J Gastroenterol* 2003;38:635-42.

109. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. *Scand J Gastroenterol* 1997;32:238-45.

110. Mandel JS, Bond JH, Bradley M, Snover DC, Church TR, Williams S, et al. Sensitivity, specificity, and positive predictivity of the Hemoccult test in screening for colorectal cancers: the University of Minnesota's Colon Cancer Control Study. *Gastroenterology* 1989;97:597-600.

111. Mant D, Fitzpatrick R, Hogg A, Fuller A, Farmer A, Verne J, et al. Experiences of patients with false positive results from colorectal cancer screening. *Br J Gen Pract* 1990;40:423-5.

112. Niv Y, Lev-El M, Fraser G, Abuksis G, Tamir A. Protective effect of faecal occult blood test screening for colorectal cancer: worse prognosis for screening refusers. *Gut* 2002;50:33-7.

113. Rasmussen M, Kronborg O, Fenger C, Jorgensen OD. Possible advantages and drawbacks of adding flexible sigmoidoscopy to hemoccult-II in screening for colorectal cancer: a randomized study. *Scand J Gastroenterol* 1999;34:73-8.

114. Daniels K, McKee M. Options for screening for colorectal cancer in the Royal Air Force: a cost-effectiveness evaluation. *J R Army Med Corps* 1995;141:142-50.

115. Walker A, Whynes DK. Filtering strategies in mass population screening for colorectal cancer: an economic evaluation. *Med Decis Mak* 1992;12:2-7.

116. van Ballegooijen M, Habbema JDF, Boer R, Zauber AG, Brown ML, Agency for Healthcare Research Quality. *A comparison of the cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in the Medicare population*: Agency for Healthcare Research Quality, 2003.

117. Castiglione G, Zappa M, Grazzini G, Sani C, Mazzotta A, Mantellini P, et al. Cost analysis in a population based screening programme for colorectal cancer: comparison of immunochemical and guaiac faecal occult blood testing. *J Med Screen* 1997;4:142-6.

118. Berchi C, Bouvier V, Reaud JM, Launoy G. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. *Health Econ* 2004;13:227-38.

119. Shimbo T, Glick HA, Eisenberg JM. Cost-effectiveness analysis of strategies for colorectal cancer screening in Japan. *Int J Technol Assess Health Care* 1994;10:359-75.

120. Wong S, Leong AP, Leong T. Cost-effectiveness analysis of colorectal cancer screening strategies in Singapore: a dynamic decision analytic approach. *Medinfo* 2004:104-08.

121. Lang CA, Ransohoff DF. On the sensitivity of fecal occult blood test screening for colorectal cancer [comment]. *J Natl Cancer Inst* 1997;89:1392-3.

122. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing: results for 68,308 subjects. *Scand J Gastroenterol* 1994;29:468-73.

123. Deville WLJM, Bezemer PD, Bouter LM. Publications on diagnostic test evaluation in family medicine journals: an optimal search strategy. *J Clin Epidemiol* 2000;53:65-9.

124. Tatsioni A, Zarin DA, Aronson N, Samson DJ, Flamm CR, Schmid C, et al. Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med* 2005;142:1048-55.

125. Wilczynski NL, Haynes RB, for the Hedges Team. EMBASE search strategies for identifying methodologically sound diagnostic studies for use by clinicians and researchers. *BMC Medicine* 2005;3.

126. Bachmann LM, Estermann P, Kronenberg C, ter Riet G. Identifying diagnostic accuracy studies in EMBASE. *J Med Libr Assoc* 2003;91:341-6.

127. Bachmann LM, Coray R, Estermann P, ter Riet G. Identifying diagnostic studies in MEDLINE: reducing the number needed to read. *J Am Med Inform Assoc* 2002;9:653–58.

128. Dickersin K, Min YI. Publication bias: the problem that won't go away. *Ann N Y Acad Sci* 1993;703:135-46; discussion 46-8.

129. Begg CB. Biases in the assessment of diagnostic tests. *Stat Med* 1987;6:411-23.

130. Begg CB, Berlin JA. Publication bias and dissemination of clinical research. *J Natl Cancer Inst* 1989;81:107-15.

131. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003;3:25.

132. Westwood ME, Whiting PF, Kleijnen J. How does study quality affect the results of a diagnostic meta-analysis? *BMC Med Res Methodol* 2005;5:20.

133. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA* 1999;282:1061-6.

134. Medical Services Advisory Committee. *Faecal occult blood testing for population health screening*. Canberra, Australia: Medical Services Advisory Committee; 2004. Report No.: MSAC reference 18.

135. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. *Clin Chem* 2003;49:1-6.

136. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;138:W1-12.

137. Austoker J. Cancer prevention in primary care: screening for colorectal cancer. *BMJ* 1994;309:382-86.

138. Macrae FA, St John DJ, Caligiore P, Taylor LS, Legge JW. Optimal dietary conditions for hemoccult testing. *Gastroenterology* 1982;82:899-903.

139. Jaffe RM, Kasten B, Young DS, MacLowry JD. False negative stool occult blood tests caused by ingestion of ascorbic acid (vitamin C). *Ann Intern Med* 1975;83:824-6.

140. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. *Med J Aust* 2001;175:195-8.

141. Radominski L, Ly P, Yeh E. Performance evaluation of hemeselect immunochemical test for fecal occult blood. *Clin Chem* 1990;36:1180.

142. Turunen MJ, Liewendahl K, Partanen P, Adlercreutz H. Immunological detection of faecal occult blood in colorectal cancer. *Br J Cancer* 1984;49:141-8.

143. Heinrich HC, Kamal R, Leberecht P. Ultrasensitive latex-agglutination-test for the specific immunochemical detection and quantification of faecal occult blood loss. *Klinische Wochenschrift* 1983;61:765-7.

144. Atkin WS. Impending or pending? The national bowel cancer screening programme. *BMJ* 2006;332:doi: 10.1136/bmj.38797.494757.47.

145. Adams EC, Layman KM. Immunochemical confirmation of gastrointestinal bleeding. *Ann Clin Lab Sci* 1974;4:343-49.

146. Hardcastle JD, Armitage NC, Chamberlain J, Balfour TW, Amar SS. A control trial of faecal occult blood screening for colorectal cancer: 2-year results. *Br J Surg* 1985;72 Suppl:S69-71.

147. Olynyk JK, Platell CF, Collett JA. Fecal occult blood and flexible sigmoidoscopy screening for colorectal cancer: modeling the impact on colonoscopy requirements and cancer detection rates. *J Gastroenterol Hepatol* 2001;16:389-92.

148. Adamsen S, Kronborg O. Acceptability and compliance in screening for colorectal cancer with fecal occult blood test. *Scand J Gastroenterol* 1984;19:531-4.

149. Hardcastle JD, Armitage NC, Chamberlain J, Amar SS, James PD, Balfour TW. Fecal occult blood screening for colorectal cancer in the general population: results of a controlled trial. *Cancer* 1986;58:397-403.

150. Ookata T. [Screening for colorectal cancers using hemoccult II testing for occult blood in the stool]. *Jpn Pharmacol Ther* 1985;13:135-40.

151. Adlercreutz H, Liewendahl K, Virkola P. Evaluation of Fecatest, a new guaiac test for occult blood in feces. *Clin Chem* 1978;24:756-61.

152. Hardcastle JD, Thomas WM, Chamberlain J, Pye G, Sheffield J, James PD, et al. Randomised, controlled trial of faecal occult blood screening for colorectal cancer: results for first 107,349 subjects. *Lancet* 1989;1:1160-4.

153. Ostrow JD, Mulvaney CA, Hansell JR, Rhodes RS. Sensitivity and reproducibility of chemical tests for fecal occult blood with an emphasis on false-positive reactions. *Am J Dig Dis* 1973;18:930-40.

154. Adlercreutz H, Virkola P. Methodological and clinical comparison of some old and new guaiac tests for occult blood in feces. *J Clin Chem Clin Bio* 1980;18:695.

155. Hardcastle J. Randomized control trial of faecal occult blood screening for colorectal cancer: results for the first 144,103 patients. *Eur J Cancer Prev* 1991;1 Suppl 2:21.

156. Otto S, Czalbert JH, Papp I, Eckhardt S. Early detection of colorectal cancer: preliminary report on the prospective value of a combined screening method for occult rectal bleeding. *Oncology* 1990;47:209-14.

157. Adlercreutz H, Partanen P, Virkola P, Liewendahl K, Turunen MJ. Five guaiac-based tests for occult blood in faeces compared in vitro and in vivo. *Scand J Clin Lab Invest* 1984;44:519-28.

158. Hardcastle JD. European trial of colorectal cancer screening comparing flexible sigmoidoscopy and faecal occult blood testing (FOBT) with FOBT alone. *Biomedical and Health Research* 1994:116-17.

159. Otto S, Dobrossy L. Screening for colorectal cancer with immunological FOBT. *Br J Cancer* 2004;90:1871-2.

160. Agusti P, Agustin S, Sandra T, Miquel N, Ricard C, Montserrat A, et al. Colorectal cancer screening (CRC) with fecal occult blood test (FOBT) and total colonoscopy. Immediate results and revision after five years. *Gastroenterology* 2004;126:A349.

161. Panzer S, Okolo P, Rai R, Giardiello F. A comparative study of hemoccult and hemoprompt, a self developing fecal occult blood test. *Gastroenterology* 1995;108 (4 Suppl):A28.

162. Ahlquist DA, Klee GG, McGill DB, Ellefson RD. Colorectal cancer detection in the practice setting: impact of fecal blood testing. *Arch Intern Med* 1990;150:1041-45.

163. Hart AR, Gay SP, Donnelly A, Griffin L, Inglis A, Mayberry MK, et al. Screening for colorectal cancer in Market Harborough, UK: a community-based programme. *Eur J Gastroenterol Hepatol* 1994;6:519-22.

164. Parikh A, Ramamoorthy R, Igwegbe I, Holland BK, Houghton J. In-office hemoccult screening is comparable to three-day-at-home testing: a study in cost effectiveness, compliance and outcomes in an inner city population. *Gastroenterology* 2000;118:A266.

165. Rattan J, Rozen P, Ron E, Fireman Z, Hallak A, Grossman A, et al. The relative and complementary value of fecal occult blood tests and flexible sigmoidoscopy in screening for large bowel neoplasia. *Am J Gastroenterol* 1986;81:888.

166. Hart AR, Barone TL, Gay SP, Inglis A, Griffin L, Tallon CA, et al. The effect on compliance of a health education leaflet in colorectal cancer screening in general practice in central England. *J Epidemiol Community Health* 1997;51:187-91.

167. Parra-Blanco A, Gimeno A, Nicolas D, Deniz D, Grosso B, Garcia M, et al. Efficacy of an immunological fecal occult blood test for colorectal cancer screening in a southern European population. *Gastroenterology* 2004;126:A348.

168. Ahlquist DA, Wieand HS, Moertel CG, McGill DB, Loprinzi CL, O'Connell MJ, et al. Accuracy of fecal occult blood screening for colorectal neoplasia: a prospective study using Hemoccult and HemoQuant tests. *JAMA* 1993;269:1262-7.

169. Hart AR, Eaden J, Barnett S, de Bono AM, Mayberry JF. Colorectal cancer prevention: an approach to increasing compliance in a faecal occult blood test screening programme. *J Epidemiol Community Health* 1998;52:818-20.

170. Pavlides GP, Milligan FD, Clarke DN, Cohen SB, Wennstrom CJ, Burbige EJ, et al. Hereditary polyposis coli I: the diagnostic value of colonoscopy, barium enema, and fecal occult blood. *Cancer* 1977;40:2632-9.

171. Aisawa T, Munakata A. Early detection of colorectal cancer. *Nippon Daicho Komonbyo Gakkai Zasshi* 1980;33:292.

172. Hart AR, Glover N, Howick-Baker J, Mayberry JF. An industry based approach to colorectal cancer screening in an asymptomatic population. *Postgrad Med J* 2003;79:646-9.

173. Ajam M, Ramanujam LS, Gandhi VC, Leehey DJ, Ing TS, Schnell TG, et al. Colon-cancer screening in dialysis patients. *Artif Organs* 1990;14:95-7.

174. Hastings JB. Mass screening for colorectal cancer. *Am J Surg* 1974;127:228-33.

175. Petrelli NJ, Palmer M, Michalek A, Herrera L, Mink I, Bersani G, et al. Massive screening for colorectal cancer: a single institution's public commitment. *Arch Surg* 1990;125:1049-51.

176. Akagi K. [A study on establishment of suitable mass survey for colorectal cancer]. *Kawasaki Igakkai Shi* 1993;19:381-92.

177. Hatfield AK, Bozinovich M, Steiner J, Alster JM, Imrey B. Carle clinic colon cancer detection project. *Proc Amer Soc Clin Oncol* 1983;2:C15.

178. Petrelli N, Michalek AM, Freedman A, Baroni M, Mink I, Rodriguez-Bigas M. Immunochemical versus guaiac occult blood stool tests: results of a community-based screening program. *Surg Oncol* 1994;3:27-36.

179. Ali M, Yaqub M, Haider Z, Anees I, Bhargava S, Gian J. Yield of dual endoscopy for positive fecal occult blood test. *Am J Gastroenterol* 2003;98:82-5.

180. Heeb MA, Ahlvin RC. Screening for colorectal carcinoma in a rural area. *Surgery* 1978;83:540-1.

181. Porschen R, Kruis W, Strohmeyer G. Fecal occult blood testing: comparative evaluation of a two-hole versus a three-hole single slide test. *Hepatogastroenterology* 1993;40:191-3.

182. Allison JE, Tekawa I, Ransom L, Adrain A. Combination fecal occult blood test (Hemoccult II SENSA-HemeSelect): a promising alternative to Hemoccult II for detection of CR neoplasms in mass screening of average risk patients. *Gastroenterology* 1992;102 Suppl:A340.

183. Heim CR, Rhodes DF, Burger MC, Spickard WA. Evaluation of positive Hemoccult test results obtained in a community screening program. *J Tenn Med Assoc* 1986;79:755-8.

184. Prassler R, Behr W, Barnert J, Wienbeck M. [Validity of an immunological test for fecal occult blood (latex agglutination)]. *Klinisches Labor* 1992;38:694-96.

185. Allison JE, Tekawa I, Ransom L, Adrain A. Hemoccult II sensa: an impractical mass screening test for colorectal neoplasms in racially diverse populations. *Gastroenterology* 1993;104:A384.

186. Helfrich GB, Petrucci P, Webb H. Mass screening for colorectal cancer. *JAMA* 1977;238:1502-3.

187. Preisich P, Siba S, Szakatsy E. Mass screening for colorectal cancer in Hungary. *J R Soc Med* 1987;80:352-3.

188. Herrinton LJ, Selby JV, Friedman GD, Quesenberry CP, Weiss NS. Case-control study of digital-rectal screening in relation to mortality from cancer of the distal rectum. *Am J Epidemiol* 1995;142:961-4.

189. Protell RL. Hemoccult testing: the most sensitive practical screening test for colorectal carcinoma: a cooperative study. *Clin Res* 1979;27:A28.

190. Angelici A, Piermattei A, Palumbo P, Turano R, Vietri F. [The guaiac test and colorectal pathology: clinical evaluation]. *Minerva Chir* 1993;48:273-6.

191. Herzog P, Schreiber HJ, Preiss JP, Ewe K, Fischer J, Holtermueller KH. Sensitivitat des haemocculttests bei blutung kolorektaler polypen ein vergleich mit der radiochrommethode. *Z Gastroenterol* 1979;9:602-03.

192. Pye G, Ballantyne KC, Armitage NC, Hardcastle JD. Influence of non-steroidal anti-inflammatory drugs on the outcome of faecal occult blood tests in screening for colorectal cancer. *Br Med J (Clin Res Ed)* 1987;294:1510-1.

193. Armbrecht U, Manus B, Bragelmann R, Stockbrugger RW, Stolte M. Acceptance and outcome of endoscopic screening for colonic neoplasia in patients undergoing clinical rehabilitation for gastrointestinal and metabolic diseases. *Z Gastroenterol* 1994;32:3-7.

194. Herzog P, Ebener B, Holtermueller KH. Testung auf okkultes blut in stuhl: ist eine verlangerung der testperiode von 3 auf 6 tage sinnvoll? Ergebnisse einer prospektiven studie. *Z Gastroenterol* 1983;21:393-94.

195. Qin DX, Huang QH, Zh SJ, Mo H, Zou XN. Screening of hollow organ tumours by occult blood test. *Eur J Cancer Prev* 2000;9:367-69.

196. Armbrecht U, Manus B, Bragelmann R, Stockbrugger R. Screening for colorectal neoplasia (CRN): comparison of two methods. *Gastroenterology* 1995;108 (4 Suppl):A446.

197. Herzog P, Busse E, Holtermuller KH. Testing the sensitivity of immunological tests in the occurrence of blood in the stool (latex agglutination). *Z Gastroenterol* 1985;23:446.

198. Racz I, Szabo A, Goda M, Olah A. Preliminary colorectal cancer screening program model in Hungary. *Gastrointestinal Oncology* 2002;4:119-21.

199. Armitage NC, Amar SS, Balfour TW, Hardcastle JD. Controlled comparison of the fecal occult blood tests haemoccult and fecatwin feca EIA in population screening for colorectal cancer. *Gut* 1984;25:A568-A69.

200. Higuma S, Matsuda S, Takeda N, Kimura M, Miyake M, Karai I, et al. [Mass screening for colorectal cancer in local inhabitants]. *Kawasaki Igakkai Shi* 1994;20:13-17.

201. Armitage N, Hardcastle JD, Amar SS, Balfour TW, Haynes J, James PD. A comparison of an immunological faecal occult blood test Fecatwin sensitive/FECA EIA with Haemoccult in population screening for colorectal cancer. *Br J Cancer* 1985;51:799-804.

202. Hirobe K, Owaki T, Matsuzawa Y. [7 years of annual mass screening for colorectal cancer in office workers: usefulness of 3-day RPHA method]. *Sangyo Eiseigaku Zasshi* 1995;37:187-94.

203. Rae AJ, Cleator IGM. The two-tier fecal occult blood test: cost-effective screening. *Can J Gastroenterol* 1994;8:362-68.

204. Armitage NC. Two-year results of the Nottingham trial. *Int J Colorectal Dis* 1986;1:71-72.

205. Hisamichi S, Fukao A, Fujii Y, Tsuji I, Komatsu S, Inawashiro H, et al. Mass screening for colorectal cancer in Japan. *Cancer Detect Prev* 1991;15:351-6.

206. Rae LC. Community screening for colorectal cancer in north-eastern New South Wales, 1987-1996. *Med J Aust* 1998;168:382-5.

207. Armitage N, Hardcastle J, Leicester R. Screening for colorectal cancer. *Practitioner* 1989;233:830, 32-3.

208. Hiwatashi N, Morimoto T, Fukao A, Sato H, Sugahara N, Hisamichi S, et al. An evaluation of mass screening using fecal occult blood test for colorectal cancer in Japan: a case-control study. *Jpn J Cancer Res* 1993;84:1110-2.

209. Raine M, LaVigne R. Fecal occult blood screening in northern Idaho. *J Fam Pract* 1987;25:611-2.

210. Aroasio E, Rossini FP. Sensitivity evaluation of three different tests for faecal occult blood detection. *Tumour Biol* 1997;18 Suppl 1:93.

211. Hiwatashi N, Shimada T. [Faecal occult blood test and mass screening for colorectal cancer]. *Nippon Rinsho* 2003;61:201-6.

212. Ramsey SD, Mandelson MT, Berry K, Etzioni R, Harrison R. Cancer-attributable costs of diagnosis and care for persons with screen-detected versus symptom-detected colorectal cancer. *Gastroenterology* 2003;125:1645-50.

213. Aste H, Pugliese V, Giacchero A, et al. [Is Hemoccult a good test for colorectal polyps detection?]. *Acta Endoscopica* 1980;10:343-47.

214. Hoerr SO, Bliss WR, Kauffman J. Clinical evaluation of various tests for occult blood in the feces. *J Am Med Assoc* 1949;141:1213-7.

215. Rasmussen M, Fenger C, Kronborg O. Diagnostic yield in a biennial Hemoccult-II screening program compared to a once-only screening with flexible sigmoidoscopy and Hemoccult-II. *Scand J Gastroenterol* 2003;38:114-8.

216. Bahrt KM, Korman LY, Nashel DJ. Significance of a positive test for occult blood in stools of patients taking anti-inflammatory drugs. *Arch Intern Med* 1984;144:2165-6.

217. Hofbauer F, Mach K, Egermann G. Repeated mass screening for colorectal neoplasms by means of the fecal occult blood test in a country district. (Results of an Information Campaign). *Wien Klin Wochen* 1991;103:288-95.

218. Baig NA, Weinberg DS, Myers R, Turner B, Hyslop T. Inadequate follow-up of positive fecal occult blood test results: Survey of physician-reported reasons. *Gastroenterology* 2001;120:350.

219. Hoff G, Grotmol T, Thiis-Evensen E, Bretthauer M, Gondal G, Vatn MH. Testing for faecal calprotectin (PhiCal) in the Norwegian Colorectal Cancer Prevention trial on flexible sigmoidoscopy screening: comparison with an immunochemical test for occult blood (FlexSure OBT). *Gut* 2004;53:1329-33.

220. Ratto C, Forni F, Sofo L, Nucera P, Ippoliti M, Bossola M, et al. Comparison between different faecal occult blood tests in neoplastic and inflammatory diseases of the large bowel. *Acta Med Rom* 1992;30:386-87.

221. Baker J, Carlson D, Ly P, Olivet E, Rampal S. Readability and sensitivity of two guaiac-based fecal occult blood tests. *Gastroenterology* 1988;94:A18.

222. Hoffman A, Young Q, Bright-Asare P, Abcarian H, Fitzpatrick J, Lidow E, et al. Early detection of bowel cancer at an urban public hospital: demonstration project. *CA Cancer J Clin* 1983;33:344-58.

223. Reilly JM, Ballantyne GH, Fleming FX, Zucker KA, Modlin IM. Evaluation of the occult blood test in screening for colorectal neoplasms: a prospective study using flexible endoscopy. *Am Surg* 1990;56:119-23.

224. Bampton P, Sandford J, Cadd B, Cole S, Young G. Interval annual faecal occult blood testing detects further lesions in a colonoscopy-based screening surveillance program. *Gastroenterology* 2002;122:A589-A90.

225. Honda K, Ishiwata Y, Ebine S. [Result of mass screening for colorectal cancer and some problems of barium enema X-ray examination]. *Ther Res* 1995;16 Suppl 2:60-64.

226. Rennert G, Rennert HS, Miron E, Peterburg Y. Population screening with fecal occult blood test. *Cancer Epidemiol Biomarkers Prev* 2000;9:236.

227. Bampton P, Sandford J, Cole S, Smith A, Morcom J, Cadd B, et al. Interval fecal occult blood testing in a colonoscopy-based colorectal cancer surveillance program detects additional pathology. *Gastroenterology* 2004;126:A25.

228. Hope RL, Chu G, Hope AH, Newcombe RG, Gillespie PE, Williams SJ. Comparison of three faecal occult blood tests in the detection of colorectal neoplasia. *Gut* 1996;39:722-5.

229. Rex DK, Lehman GA, Hawes RH, Ulbright TM, Smith JJ. Screening colonoscopy in asymptomatic average-risk persons with negative fecal occult blood tests. *Gastroenterology* 1991;100:64-7.

230. Barber MD, Abraham A, Brydon WG, Waldron BM, Williams AJ. Assessment of faecal occult blood loss by qualitative and quantitative methods. *J R Coll Surg Edinb* 2002;47:491-4.

231. Howarth GF, Robinsonm MH, Hardcastle JD, Logan RF. The use of age, symptoms and faecal occult blood (FOB) testing in the prediction of colorectal neoplasia. *Gastroenterology* 2000;118:A260-A61.

232. Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, et al. Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history. *Am J Gastroenterol* 1993;88:825-31.

233. Barbot L, Gobert JG, Kapel N. Faecal occult blood testing: comparison of a latex agglutination test (Hemolexo) and an immunoturbidimetric test (QuikRead FOB). *Ann Biol Clin (Paris)* 2004;62:339-43.

234. Humphery TJ, Goulston K. Chemical testing of occult blood in faeces: "haematest", "occultest", and guaiac testing correlated with chromium estimation of faecal blood loss. *Med J Aust* 1969;1:1291-3.

235. Ribet A, Frexinos J, Escourrou J, Delpu J. [Controlled study of hemoccult in the diagnosis of colorectal tumors]. *Gastroenterol Clin Biol* 1979;3:309-10.

236. Barnett RN. The guaiac test: correlation with clinical findings. *Gastroenterology* 1952;21:540-43.

237. Imai N, Hayashi C. The evaluation of rapid tests for detection of occult blood in feces. *J Am Med Technol* 1979;41:289-92.

238. Ribet A, Escourrou J, Frexinos J, Delpu J. Screening for colorectal tumors: results of two years experience. *Cancer Detect Prev* 1980;3:449-61.

239. Barrison IG, Littlewood ER, Primavesi J, et al. Screening for occult gastrointestinal bleeding in hospital patients. *J R Soc Med* 1981;74:41-43.

240. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Effect of a prior colorectal screening or diagnostic test on findings at screening colonoscopy. *Gastroenterology* 2001;120 (5 Suppl 1):A405.

241. Richardson JL. Colorectal cancer: a mass screening and education program. *Geriatrics* 1977;32:123-31.

242. Barrison IG, Parkins RA. Assessment of Fecatest and Haemoccult for faecal occult blood testing. *Br Med J (Clin Res Ed)* 1982;285:1356.

243. Ishii K, Sengoku M, Oku K, Sakita R, Kawai I, Nagai K, et al. [Evaluation of immunological fecal occult blood test and simultaneously combined method of sigmoidoscopy and barium enema for colorectal cancer screening]. *Ther Res* 1990;11 Suppl 2:201-05.

244. Riedel H, Heyer I, Schumann K, Helmstaedt D, Otto P. [Hemoccult tests of the stool at the time of preventive gynaecological examination]. *Geburtshilfe Frauenheilkd* 1977;37:27-35.

245. Barrison IG, Parkins RA. The clinical value of Haemoccult and Fecatwin in the detection of colorectal neoplasia in hospital and general practice patients. *Postgrad Med J* 1985;61:701-4.

246. Ishikawa M, Ozima I, Yamagata H, Akimoto M, Kurihara T, Takada M, et al. [The immunological fecal occult blood test in the periodic medical check-up: the 2nd report]. *Ther Res* 1990;11 Suppl 2:210-13.

247. Riegler G, Di Carlo V, Iavicoli N, Troisi V, Forlani G. [A decade of experience in rescreening for colonic cancer in a working population]. *Minerva Dietol Gastroenterol* 1990;36:105-8.

248. Bartnik W, Butruk E, Tomecki R, Ruzyllo E. [Screening for neoplasms of the large bowel using the hemoccult test]. *Pol Arch Med Wewn* 1982;67:153-9.

249. Isley Jr JK, Akin RB. A community-based colon and rectal cancer screening program. *J Fla Med Assoc* 1981;68:501-04.

250. Robertson JD, Maughan RJ, Davidson RJ. Correlation between qualitative and quantitative faecal occult blood tests. *Clin Chim Acta* 1987;170:339-43.

251. Bartnik W, Cwikla M, Regula J, Tomecki R, Butruk E. [Results of the Haemoccult test in neoplasms and other diseases of the digestive system]. *Pol Arch Med Wewn* 1986;76:193-8.

252. Ito M, Sigaku M, Shimono M, et al. [Report of mass screening for colorectal cancer in our corporate group]. *Matsushita Med J* 1990;29:203-10.

253. Robinson MHE, Berry DP, Vellacott KD, Moshakis V, Hardcastle JD. A randomised trial of flexible sigmoidoscopy and hemoccult vs hemoccult alone in colorectal cancer population screening. *Gut* 1993;34:S40.

254. Bassett ML, Goulston KJ. False positive and negative hemoccult reactions on a normal diet and effect of diet restriction. *Aust N Z J Med* 1980;10:1-4.

255. Iwase T, Bandou H, Hayashi H. [Problems of fecal occult blood tests in screening for colorectal cancer and measures to detect false negative cancer at its early stage]. *Ther Res* 1990;11 Suppl 2:46-50.

256. Robinson MH, Marks CG, Farrands PA, Thomas WM, Hardcastle JD. Population screening for colorectal cancer: comparison between guaiac and immunological faecal occult blood tests. *Br J Surg* 1994;81:448-51.

257. Bassil MA, Zummer K, Domont A. [Tracking the colo-rectal cancer with Hemoccult II test: first results in an occupational medical service]. *Arch Mal Prof Med Trav* 1998;59:507-09.

258. Iwase N, Oya M, Yanagida T, Hirayasu Y, Ishii Y, Kubota T, et al. [Immunological fecal occult blood test in patients with anal diseases]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1995;48:1065-69.

259. Robinson MH, Moss SM, Hardcastle JD, Whynes DK, Chamberlain JO, Mangham CM. Effect of retesting with dietary restriction in Haemoccult screening for colorectal cancer. *J Med Screen* 1995;2:41-4.

260. Bat L, Pines A, Ron E, Niv Y, Arditi E, Shemesh E. A community-based program of colorectal screening in an asymptomatic population: evaluation of screening tests and compliance. *Am J Gastroenterol* 1986;81:647-51.

261. Jacobi D. Darmkrebs-fruherkennungsstudie Molln, 1979: bericht uber eine beispielhafte krebs-fruherkennungsaktion. *Krebsmedizin* 1980;1:5-9.

262. Robra BP. The Statutory Health Insurance Screening Programme in the Federal Republic of Germany. *Int J Colorectal Dis* 1986;1:66-68.

263. Bech K, Kronborg O, Fenger C. Adenomas and hyperplastic polyps in screening studies. *World J Surg* 1991;15:7-13.

264. Jankovic S, Kostic Z, Marinkovic J, Radovanovic Z. [Use of the hemoccult test in the detection of colorectal cancer]. *Vojnosanit Pregl* 1994;51:220-3.

265. Rocchi L. [Preliminary notes on the possibility of screening for colonic and rectal cancer]. *Minerva Med* 1982;73:3119-21.

266. Bech K, Kronborg O. [Requirement of hospital beds in connection with screening for colorectal cancer: the first 5-years of a randomized population survey]. *Ugeskr Laeger* 1992;154:696-9.

267. Jeanson A, Jamart J, Maisin JM, Vanheuverzwyn R, Gohy P, Debongnie JC, et al. Assessment of the new immunological test Hemoblot for detecting occult blood in faeces. *Eur J Cancer Prev* 1994;3:407-12.

268. Rockey DC, Koch J, Cello JP, Sanders LL, McQuaid K. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood tests. *N Engl J Med* 1998;339:153-9.

269. Bedenne L, Faivre J, Durand G, Milan C, Boutron MC, Klepping C. [Detection of colorectal cancer by the Hemoccult test: preliminary results of a controlled study in Burgundy]. *Gastroenterol Clin Biol* 1989;13:A1.

270. Jensen J, Kewenter J, Haglind E, Lycke G, Svensson C, Ahren C. Diagnostic accuracy of double-contrast enema and rectosigmoidoscopy in connection with faecal occult blood testing for the detection of rectosigmoid neoplasms. *Br J Surg* 1986;73:961-4.

271. Ross TH, Johnson JCM. Detecting colorectal cancer. *Ariz Med* 1976;33:445-48.

272. Bedenne L, Durand G, Faivre J, Milan C, Boutron MC, Arveux P, et al. [Preliminary results of a mass screening program for colorectal cancer]. *Gastroenterol Clin Biol* 1990;14:140-5.

273. Jensen J, Kewenter J, Asztely M, Lycke G, Wojciechowski J. Double contrast barium enema and flexible rectosigmoidoscopy: a reliable diagnostic combination for detection of colorectal neoplasm. *Br J Surg* 1990;77:270-2.

274. Roth A, Roguljic A, Vujicic N. [The results of Hemoccult Test in 200 patients with gastrointestinal cancer]. *Lijec Vjesn* 1982;104:115-9.

275. Benesova A, Fric P, Zavoral M, Kocna P, Matejovic F, Vokracka V, et al. [Comparison of immunochemical and biochemical tests for occult hemorrhage in feces]. *Cas Lek Cesk* 1993;132:523-5.

276. Jensen BM, Kronborg O, Fenger C. Interval cancers in screening with fecal occult blood test for colorectal cancer. *Scand J Gastroenterol* 1992;27:779-82.

277. Rozen P, Fireman Z, Terdiman R, Hellerstein SM, Rattan J, Gilat T. Selective screening for colorectal tumors in the Tel-Aviv area: technique and initial results. In: Winawer SJ, Schottenfeld D, Sherlock P, editors. *Colorectal cancer: prevention, epidemiology and screening*. New York: Raven Press; 1980. p. 275-83.

278. Benn HP, Heinrich HC. Diagnosticher wert kommerzieller okkultblut-teste. In: *96 Tagg. Nordwestdeutsche Gesellschaft fur Innere Medizin*; 1981 Jan 22-24; Hamburg. Verlagsk; Lubeck; 1981. p. 63-65.

279. Jensen J, Kewenter J, Swedenborg J. The correlation of symptoms, occult blood tests, and neoplasms in patients referred for double-contrast barium enema. *Scand J Gastroenterol* 1993;28:911-4.

280. Rozen P, Fireman Z, Hallak A, Grossman A, Rattan J, Gilat T, et al. The relative value of fecal occult blood tests and flexible sigmoidoscopy in screening for large bowel neoplasia. *Gastrointest Endosc* 1986;32:166.

281. Mahendra Raj S. Fecal occult blood testing of Trichuris-infected primary school children in northeastern peninsular Malaysia. *American Journal of Tropical Medicine & Hygiene* 1999;60:165-66.

282. Jensen BM, Holtved E, Kronborg O, Norgard JR, Fenger C. [Rectoscopy and Hemoccult-II as initial diagnosis: a procedure in patients with symptoms of irritable colon]. *Ugeskr Laeger* 1994;156:4795-7, 800.

283. Rozen P, Ron E, Fireman Z, Hallak A, Grossman A, Baratz M, et al. The relative value of fecal occult blood tests and flexible sigmoidoscopy in screening for large bowel neoplasia. *Cancer* 1987;60:2553-8.

284. Beretta KR, Guller R, Singeisen M, Stalder GA. [Occult blood in feces: a prospective study for the comparison of Hemoccult and Fecatest]. *Schweiz Med Wochenschr* 1978;108:1905-7.

285. Jorgensen OD, Kronborg O, Fenger C. A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut* 2002;50:29-32.

286. Rozen P. Screening for colorectal neoplasia in the Tel Aviv area: cumulative data 1979-89 and initial conclusions. *Isr J Med Sci* 1992;28:8-20.

287. Berry DP, Clarke P, Hardcastle JD, Vellacott KD. Randomized trial of the addition of flexible sigmoidoscopy to faecal occult blood testing for colorectal neoplasia population screening. *Br J Surg* 1997;84:1274-6.

288. John M, Schmidt-Gayk H, Arndt B, Theuer D. [Screening for occult blood by fecal albumin: comparison of two immunological tests]. *Klinisches Labor* 1994;40:77-81.

289. Rozen P, Knaani J, Papo N. Evaluation and comparison of an immunochemical and a guaiac faecal occult blood screening test for colorectal neoplasia. *Eur J Cancer Prev* 1995;4:475-81.

290. Bertario L, Severini A, Mantero M, et al. Diagnosis of asymptomatic colorectal cancer using a stabilized guaiac test (Hemoccult) for detecting occult blood in stools: preliminary results. *Ital J Gastroenterol* 1979;11:53-55.

291. Johne B, Kronborg O, Ton HI, Kristinsson J, Fuglerud P. A new fecal calprotectin test for colorectal neoplasia: clinical results and comparison with previous method. *Scand J Gastroenterol* 2001;36:291-96.

292. Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. *Dig Dis Sci* 1997;42:2064-71.

293. Bertario L, Berrino F, Severini A, Pizzetti P, Sala P, Mirabile V, et al. Early detection of colon cancer, using the guaiac-test (Hemoccult), two years experience. *Hepatogastroenterology* 1980;27 Suppl:S99.

294. Johnson CD, Harmsen W, Wilson LA, MacCarty RL, Welch TJ, Ahlquist DA. Comparison of CT colonography with colonoscopy, flexible sigmoidoscopy, and fecal occult blood testing for screen-detection of colorectal polyps. *Radiology* 2002;225:444.

295. Rozen P, Samuel Z, Knaani J. Comparative specificities of a guaiac and an immunochemical fecal occult blood test and elimination of dietary restrictions. *Gastrointest Endosc* 1998;47:317.

296. Bertario L, Russo A, Crosignani P, Sala P, Spinelli P, Pizzetti P, et al. Reducing colorectal cancer mortality by repeated faecal occult blood test: a nested case-control study. *Eur J Cancer* 1999;35:973-7.

297. Jorge AD, Sanchez D, Diaz M, Lorenzo J, Milutin C. [Early detection of colonic and rectal cancer; extensive study of occult blood]. *Acta Gastroenterol Latinoam* 1977;7:261-8.

298. Rozen P, Samuel Z, Knaani J. Choosing a fecal occult blood test (FOBT) for a population colorectal screening program. *Gastroenterology* 1999;116:A493.

299. Besancon F. Placeboccult: efficacite et cout dans le depistage ou la prevention des cancers coliques et rectaux. *Hepatogastroenterology* 1980;27 Suppl:S229.

300. Edelist DD. Does fecal occult blood screening reduce colorectal cancer morbidity? *J Fam Pract* 2002;51:412.

301. Rozen P, Knaani J, Samuel Z. Eliminating the need for dietary restrictions when using a sensitive guaiac fecal occult blood test. *Dig Dis Sci* 1999;44:756-60.

302. Bhattacharya I, Sack EM. The prevalence of adenoma and cancer at screening colonoscopy compared with colonoscopy directed by a positive hemoccult in average risk asymptomatic adults ages 60-75. *Gastroenterology* 1998;114:A566.

303. Joseph A. Compliance with fecal occult blood testing: the role of restrictive diets. *Am J Public Health* 1988;78:839-41.

304. Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. *Cancer* 2000;89:46-52.

305. Biedermann H, Schwamberger K, Troyer E. Ergebnisse einer reihenuntersuchung mit dem haemoccult-test. *Therapiewoche* 1979;29:3366-68.

306. Jouve JL, Remontet L, Dancourt V, Lejeune C, Benhamiche AM, Faivre J, et al. Estimation of screening test (Hemoccult) sensitivity in colorectal cancer mass screening. *Br J Cancer* 2001;84:1477-81.

307. de Ruiter P. [Occult blood loss and early diagnosis of colonic and rectal carcinoma]. *Ned Tijdschr Geneeskd* 1978;122:365-9.

308. Bini EJ, Rajapaksa RC, Weinshel EH. The findings and impact of nonrehydrated guaiac examination of the rectum (FINGER) study: a comparison of 2 methods of screening for colorectal cancer in asymptomatic average-risk patients. *Arch Intern Med* 1999;159:2022-6.

309. Kaneko E, Kumagai J, Hanai H, Honda N, Baba S, Kanno T. [Clinical evaluation of immunochemical fecal occult blood test]. *Nippon Shokakibyo Gakkai Zasshi* 1984;81:2930-4.

310. Saggioro A, Digilio A, Scassola M, Castelli F, Pallini P, Chiozzini G, et al. A mass screening programme for colorectal cancer in Venice, acceptability for fecal occult blood (FOB) testing in two unselected populations. *Ital J Gastroenterol* 1987;19:57-58.

311. Bini EJ, Weinshel EH, Generoso R, Salman L, Dahr G, Pena-Sing I, et al. Outcome of fecal occult blood testing obtained at the time of hospital admission. *Gastroenterology* 2000;118:A256.

312. Kanzler G, Willems D. Der haemoccult-test und die folgeuntersuchungen im bereich praktischer gastroenterologie. In: Goerttler K, editor. *Kolorektale krebsvorsorge*. Nurnberg: Wachholz; 1978. p. 99-101.

313. Saito H, Tsuchida S, Fukushi M, Kakizaki R, Aisawa T, Munakata A, et al. [An immunological test for fecal occult blood by counter immunoelectrophoresis: second report. Comparison in sensitivity to detect hemoglobin and positive reactions immunodiffusion and hemoccult test]. *Nippon Shokakibyo Gakkai Zasshi* 1984;81:2935-9.

314. Birkner BR, Altenhofen L, Brenner G, Hofstaedter F, Bredenkamp R, Riemann JF. Increase in population attendency rate for colorectal cancer screening by FOBT effects a fouvaroble cancer stage shift. *Gastroenterology* 2000;118:A720.

315. Kapparis A, Frommer D. Immunological detection of occult blood in bowel cancer patients. *Br J Cancer* 1985;52:857-61.

316. Saito H, Tsuchida S, Kakizaki R, Fukuchi M, Sano M, Aisawa T, et al. Immunochemical fecal occult blood test for mass screening of colorectal cancer by reversed passive hemaggutination (RPHA). *Jpn J Gastroenterol* 1984;81:2831.

317. Warm K, Blazek Z, Weithofer G, Bloch R. [The value of the guaiac test in the early diagnosis of gastrointestinal neoplasms]. *Verh Dtsch Ges Inn Med* 1976;82:1020-2.

318. Kaye JA, Shulman LN. Screening program for colorectal cancer: effect on stage distribution. *HMO Pract* 1992;6:13-5.

319. Saito H, Soma Y, Koeda J, Wada T, Kawaguchi H, Sobue T, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test: a case-control study. *Int J Cancer* 1995;61:465-9.

320. Bond JH, Gilbertsen VA. Early detection of colonic carcinoma by mass screening for occult stool blood: preliminary report. *Gastroenterology* 1971;72:A-8/1031.

321. Keller R, Schatzle A, Flieger D, Christl SU, Fischbach W. Better acceptance of Fecal Occult Blood Test (FOBT) for colorectal cancer screening during hospitalization. *Z Gastroenterol* 2003;41:655-8.

322. Saito H, Soma Y, Nakajima M, Koeda J, Kawaguchi H, Kakizaki R, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep* 2000;7:815-9.

323. Bond JH. The University of Minnesota Colon Cancer Control Study: current status and future plans. *Int J Colorectal Dis* 1986;1:69-70.

324. Kemppainen M, Hakkinen I, Raiha I, Pomoell R, Sourander L. Finding colorectal tumours with an immunological faecal occult blood test in symptomatic primary health care patients. *Age Ageing* 1994;23:365-70.

325. Saitoh O, Kojima K, Kayazawa M, Sugi K, Tanaka S, Nakagawa K, et al. Comparison of tests for fecal lactoferrin and fecal occult blood for colorectal diseases: a prospective pilot study. *Intern Med* 2000;39:778-82.

326. Bouvier V, Launoy G, Herbert C, Lefevre H, Maurel J, Gignoux M. Colorectal cancer after a negative Haemoccult II test and programme sensitivity after a first round of screening: the experience of the Department of Calvados (France). *Br J Cancer* 1999;81:305-9.

327. Kewenter J, Svanvik J, Svensson C, Wallgren K. The diagnostic value of the hemoccult as a screening test in patients taking anticoagulants. *Cancer* 1984;54:3054-8.

328. Sangster JF, Gerace TM, Bass MJ. Acceptability of a faecal occult blood screening protocol for carcinoma of the colon in family practice. *Fam Pract* 1986;3:246-50.

329. Bouvier V, Herbert C, Lefevre H, Launoy G. Stage of extension and treatment for colorectal cancer after a negative test and among non-responders in mass screening with guaiac faecal occult blood test: a French experience. *Eur J Cancer Prev* 2001;10:323-6.

330. Kewenter J, Svensson C, Bjorck S, Haglind E, Jensen J, Smith L, et al. Screening for detection of colorectal cancer with fecal occult blood testing. *Gastroenterology* 1985;88:1445.

331. Sasaki K, et al. [Study on immunological fecal occult blood test by hemoglobin quantification method]. *Ther Res* 1993;14 Suppl 2:246-50.

332. Bradshaw PA, Fitzgerald D, Baddam S, Stephens L, Doe J, Hua J, et al. A rapid immunochemical Flexsure(Tm) fecal occult blood test. *Clin Chem* 1995;41:S51.

333. Kewenter J, Haglind E, Jensen J, Lycke G, Svensson C. The diagnostic accuracy of double-contrast barium enema and rectosigmoidoscopy (60 cm) in subjects with a positive fecal occult blood test. *Dig Dis Sci* 1986;31:S234.

334. Sasaki K, Kunimoto M, Hirata K. Relationship between the fecal occult blood test and benign anal disorders. *Hepatogastroenterology* 2001;48:445-7.

335. Bralow SP, Kopel J. Hemoccult screening for colorectal cancer: an impact study on Sarasota, Florida. *J Fla Med Assoc* 1979;66:915-9.

336. Kewenter J, Bjork S, Haglind E, Smith L, Svanvik J, Ahren C. Screening and rescreening for colorectal cancer: a controlled trial of fecal occult blood testing in 27,700 subjects. *Cancer* 1988;62:645-51.

337. Sato H, Hiwatashi N, Miura M, Nakajima K, Yamazaki H, Suzuki K, et al. [Five years' experience of mass screening for colorectal cancer using fecal occult blood test and questionnaires]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1989;42:498-504.

338. Bradstatter G, Kratochvil P. [Early diagnosis of colonic-rectal neoplasms by detecting occult blood in the feces]. *Wien Med Wochenschr* 1978;128:209-10.

339. Kewenter J, Haglind E, Smith L. Value of a risk questionnaire in screening for colorectal neoplasm. *Br J Surg* 1989;76:280-3.

340. Sato H, Hiwatashi N, Sugahara N, Shibuki S, Miura M, Yamazaki H. [Two years' experience of mass screening for colorectal cancer using fecal occult blood test]. *Ther Res* 1989;10 Suppl 1:376-80.

341. Brandstatter G, Kratochvil P. Fruherkennung des kolorektalen karzinoms durch nachweis von okkultem blut im stuhl. *Wien Med Wochenschr* 1978;128:209-10.

342. Kewenter J, Engaras B, Haglind E, Jensen J. Value of retesting subjects with a positive Hemoccult in screening for colorectal cancer. *Br J Surg* 1990;77:1349-51.

343. Sato H, Hiwatashi N, Morimoto T, Sugahara N, Shibuki S, Miura M, et al. [Mass screening for colorectal cancer using an immunological fecal occult blood test (Imunocult)]. *Ther Res* 1990;11 Suppl 2:127-31.

344. Brault J, Favre H. [Evaluation in hospital practice of Fecatest, a new laboratory method for the detection of occult blood in feces]. *Schweiz Med Wochenschr* 1979;109:73-6.

345. Kewenter J, Asztely M, Engaras B, Haglind E, Svanvik J, Ahren C. A randomized trial of fecal occult blood testing for early detection of colorectal cancer: results of screening and rescreening of 51,325 subjects. In: Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC, editors. *Cancer screening*. New York: Cambridge University Press; 1991. p. 116-25.

346. Scales CD, Fein S, Samsa G, Muir A, Rockey D. The clinical utility of digital rectal examination with fecal occult blood testing upon hospital admission. *Gastroenterology* 2004;126:A348-A49.

347. Briancon S, Houot O, Deschamps JP, Siest G. Evaluation of a new screening test for colorectal cancer using the guaiac test and enzyme immunoassays. *J Clin Chem Clin Bio* 1985;23:592.

348. 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.

349. Briancon S, Houot O, de Souza M, Collin JF, Siest G, Deschamps JP. [Evaluation of an immunological test for detecting occult fecal blood for case-finding in colorectal tumors]. *Gastroenterol Clin Biol* 1987;11:194-200.

350. Kewenter J, Brevinge H, Engaras B, Haglind E, Ahren C. Follow-up after screening for colorectal neoplasms with fecal occult blood testing in a controlled trial. *Dis Colon Rectum* 1994;37:115-9.

351. Scheitel SM, Ahlquist DA, Wollan PC, Hagen PT, Silverstein MD. Colorectal cancer screening: a community case-control study of proctosigmoidoscopy, barium enema radiography, and fecal occult blood test efficacy. *Mayo Clin Proc* 1999;74:1207-13.

352. Brint SL, DiPalma JA, Herrera JL. Is a Hemoccult-positive rectal examination clinically significant? *South Med J* 1993;86:601-3.

353. Kewenter J, Brevinge H, Engaras B, Haglind E. The yield of flexible sigmoidoscopy and double-contrast barium enema in the diagnosis of neoplasms in the large bowel in patients with a positive Hemoccult test. *Endoscopy* 1995;27:159-63.

354. Schlucker A. [Early detection of colorectal carcinoma with occult blood test]. *Fortschr Med* 1999;117:20,22.

355. Britton DC, Farrands PA, Griffiths RL. Asymptomatic faecal occult blood screening: a practical solution to the diagnosis and treatment of colorectal cancer? In: Givel JC, Saegesser F, editors. *Colo-proctology*. New York: Springer; 1984. p. S73.

356. Kewenter J, Brevinge H. Endoscopic and surgical complications of work-up in screening for colorectal cancer. *Dis Colon Rectum* 1996;39:676-80.

357. Schnell T, Aranha GV, Sontag SJ, Tode R, Reid S, Chejfec G, et al. Fecal occult blood testing: a false sense of security? *Surgery* 1994;116:798-802; discussion 02-3.

358. Gerbes L, Jungst D, Kobberling J. [Does yearly fecal exam for occult blood lower colorectal cancer mortality?]. *Z Gastroenterol* 1994;32:603-6.

359. Khubchandani IT, Karamchandani MC, Kleckner FS, Sheets JA, Stasik JJ, Rosen L, et al. Mass screening for colorectal cancer. *Dis Colon Rectum* 1989;32:754-8.

360. Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002;50:840-4.

361. Burany B, Biro G, Prekajski M. [Results of hemoccult screening of 45- to 65-year-old residents of the town of Ada with the goal of early detection of malignant neoplasms of the colon and rectum]. *Med Pregl* 1985;38:77-81.

362. Kida K, et al. Analysis of annual examination of colorectal cancer by fecal occult blood reaction during 6 years in the occupation-limited population (Part 2): focusing on changes in fecal occult blood testing of cancer patients over years. *Ther Res* 1995;16 Suppl 2:208-11.

363. Schuler HO, Braungardt H. [A controlled study on the significance of occult blood test in the stool]. *MMW Munch Med Wochenschr* 1979;121:1465-8.

364. Burany B, Beretka F, Dzigurski-Sekulic N. [Results of a multiphase oncology population screening program in the community of Becej 1986-1987. I. The Hemoccult Program]. *Med Pregl* 1989;42:451-6.

365. Kikkawa N, Sasai H, Murai M, Mizuno S, Miyagawa S, Furota A. [Screening for colorectal carcinoma in AMHTS (automated multiphasic health testing and services)]. *Gan No Rinsho* 1983;29:1644-6.

366. Schwartz FW, Holstein H, Brecht JG. Kolorektale krebsfruherkennung mittels nachweis von okkultem blut im stuhl: erste ergebnisse. *Dtsch Arztebl* 1979;76:1223-28.

367. Cailhol J, Czernichow S, Mennen L, Boutron-Ruault M-C, Zarebska M, Franchisseur C, et al. [Participation and medical follow-up in screening of colorectal cancer in France within the SU.VI.MAX study]. *Rev Epidemiol Sante Publique* 2002;50:321-23.

368. Kim WR, Banerjee B. Outcome of endoscopic evaluation in patients with positive fecal occult blood test (FOBT) on digital rectal exam (DRE) without frank blood loss. *Gastrointest Endosc* 1993;39:293.

369. Schwartz FW, Holstein H, Brecht JG. Preliminary report of fecal occult blood testing in Germany. In: Winawer SJ, Schottenfeld D, Sherlock P, editors. *Colorectal cancer: prevention, epidemiology and screening*. New York: Raven Press; 1980. p. 267-70.

370. Carlsson U, Ekelund G, Eriksson R, Fork T, Janzon L, Leandoer L, et al. Evaluation of possibilities for mass screening for colorectal cancer with Hemoccult fecal blood test. *Dis Colon Rectum* 1986;29:553-7.

371. Kim HS, Suk KT, Kim JM, Choi YJ, Baik SK, Lee DK, et al. Sensitivity of combined two-time immunochemical fecal occult blood testing with examination of the distal colon for advanced colonic polyp. *Gastrointest Endosc* 2003;57:AB226.

372. Scriven AJ, Tapley EM. Coloscreen VPI test kit evaluated for detection of fecal occult blood. *Clin Chem* 1989;35:156-8.

373. Castellanos AR, Hakim B, Shafii A, Dunn C, Pezzi J, Cohen SW, et al. Colonoscopic findings based on initial indication. *Gastroenterology* 1994;106 (4 Suppl):A3.

374. Kimmig JM, Strauch M, Hallen M. Negative haemoccult test in malignant and premalignant lesions of the colon: validation of the haemoccult test with total colonoscopy. *Endoscopy* 1989;21:136-40.

375. Segnan N, Andreoni B, Bisanti L, Castiglione G, Ferrari A, Gasperoni S, et al. Comparing different screening strategies for colorectal cancer. *Gastroenterology* 2002;122:A483.

376. Castiglione G, Pacini F, Maltoni G. [Screening for colorectal neoplasms by the study of fecal occult blood]. *Quad Sclavo Diagn* 1984;20:440-50.

377. Kita MW. Reduction in colorectal cancer mortality related to annual fecal occult blood screening: 13 year follow-up of 46,000 subjects. *J Insur Med* 1993;25:138-9.

378. Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS. Effect of fecal occult blood testing on mortality from colorectal cancer: a case-control study. *Ann Intern Med* 1993;118:1-6.

379. Castiglione G, Pacini F, Palli D, et al. Haemoccult test and a self-administered questionnaire in the early diagnosis of colorectal cancer. *Ital J Gastroenterol* 1987;19:83-86.

380. Kitahara K, Matsui T, Yao, Tsuda S, Sakurai T, Yao K, et al. [Multi-logistic model analysis of sensitivity of fecal immunological occult blood test on colo-rectal tumors]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1995;48:129-36.

381. Shah V, Gladding D, Costello RM, Barkey D. Comparison of two commercially available immunological occult blood tests and a guaiac slide test. *Clin Chem* 1989;35:1162.

382. Castiglione G, Grazzini G, Ciatto S. Guaiac and immunochemical tests for faecal occult blood in colorectal cancer screening. *Br J Cancer* 1992;65:942-4.

383. Klaaborg K, Madsen MS, Sondergaard O, Kronborg O. Participation in mass screening for colorectal cancer with fecal occult blood test. *Scand J Gastroenterol* 1986;21:1180-4.

384. Shibata S, Shiroma T, Tsukiji M, Moroto K, Horimukai F, Miyaoka M, et al. Report of colon cancer detection in mass surveys using immunological occult blood test (Latex method). *J Med Syst* 1993;17:153-6.

385. Castiglione G, Biagini M, Barchielli A, Grazzini G, Mazzotta A, Salvadori P, et al. Effect of rehydration on guaiac-based faecal occult blood testing in colorectal cancer screening. *Br J Cancer* 1993;67:1142-4.

386. Klug W, Knoch HG, Voboril Z. [Screening using Krypto-Haem-SSWR for the early detection of colorectal carcinomas and adenomas]. *Sb Ved Pr Lek Fak Karlovy Univerzity Hradci Kralove Suppl* 1990;33:151-7.

387. Shida H, Ban K, Matsumoto M, Masuda K, Imanari T, Machida T, et al. Asymptomatic colorectal cancer detected by screening. *Dis Colon Rectum* 1996;39:1130-5.

388. Castiglione G, Sala P, Ciatto S, Grazzini G, Mazzotta A, Rossetti C, et al. Comparative analysis of results of guaiac and immunochemical tests for faecal occult blood in colorectal cancer screening in two oncological institutions. *Eur J Cancer Prev* 1994;3:399-405.

389. 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;115:111-4.

390. Shields HM, Weiner MS, Henry DR, Lloyd JA, Ransil BJ, Lamphier DA, et al. Factors that influence the decision to do an adequate evaluation of a patient with a positive stool for occult blood. *Am J Gastroenterol* 2001;96:196-203.

391. Castiglione G, Zappa M, Grazzini G, Mazzotta A, Biagini M, Salvadori P, et al. Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer. *Br J Cancer* 1996;74:141-4.

392. Kobayashi S, Yoshii Y, Kasugai T. [Screening for colorectal cancer]. *Stomach & Intestine* 1980;15:417-22.

393. Shiwaku Y, Mori K, Kojima K, Mori H, Taketomi H. [Study of immunological fecal occult blood test in mass screening of colon cancer: on usefulness of mixture method]. *Ther Res* 1990;11 Suppl 2:141-45.

394. Castiglione G, Zappa M, Grazzini G, Rubeca T, Turco P, Sani C, et al. Screening for colorectal cancer by faecal occult blood test: comparison of immunochemical tests. *J Med Screen* 2000;7:35-7.

395. Kobayashi S, Yoshii Y, Sugihara Y, Kasugai T. [Mass screening for colorectal cancer with fecal occult blood test in combination with gastric mass screening: preliminary reports]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1982;35:15-18.

396. Siba S. [Results of Hemoccult screening in Hungary (multicenter studies)]. *Orvosi Hetilap* 1980;121:1701-3.

397. Kobayashi S. [Mass screening for colorectal cancer with fecal occult blood test (Hemoccult)]. *Jpn Pharmacol Ther* 1985;13 Suppl 1:145-50.

398. Siba S. Experience with haemoccult screening in Hungary: a multicenter trial. *Hepatogastroenterology* 1983;30:27-9.

399. Chambers KJ, Morgan BP. Colorectal cancer and hemoccult. *Aust N Z J Surg* 1980;50:464-7.

400. Kocna P, Vanickova Z, Dvorak M. Fecal occult blood: immunochemical detection using ImmoCare test. *Clin Chem* 2001;39:S167.

401. Sieg A, John MR, Luthgens K, Schmidt-Gayk H. Screening for colorectal neoplasms with an immunological fecal occult hemoglobin and albumin test is cost-effective. *Gastroenterology* 1998;114:G2807.

402. Champeau J, Freche C, Jacquier L. [Hemoccult test: results in systematic health evaluation of the Parisian Region Central Primary Disease Insurance Desk]. *Med Chir Dig* 1978;7:423-4.

403. Komuta K, Furui J, Haraguchi M, Kanematsu T. The detection of colorectal cancer at an asymptomatic stage by screening is useful. *Hepatogastroenterology* 2000;47:1011-4.

404. Sieg A, Hertel A, John MR, Luthgens K, Schmidt-Gayk H. Screening for colorectal neoplasms with a new immunological human faecal haemoglobin and albumin test. *Eur J Cancer Prev* 1998;7:279-85.

405. Chang FC, Jackson TM, Jackson CR. Hemoccult screening for colorectal cancer. *Am J Surg* 1988;156:457-9.

406. Kronborg O, Fenger C, Olsen J, Pedersen KM. A randomized trial of screening for colorectal cancer with Hemoccult-II. *Scand J Clin Lab Invest* 1986;46:66.

407. Sieg A, Wirth A, Luthgens K, Schmidt-Gayk H. [Six years of screening for colorectal neoplasms with an immunological fecal occult hemoglobin test]. *Verdauungskrankheiten* 2002;20:114-17.

408. Chang AD, Hooper FJ, Greenwald BD. Evaluation of patient self-use of Hemaprompt, a self-developing fecal occult blood test (FOBT). *Gastroenterology* 1997;112:A9.

409. Kronborg O, Fenger C, Olsen J, Pedersen KM. Preliminary report on a randomized trial of screening for colorectal cancer with hemoccult-II. *Scand J Gastroenterol* 1986;21:23-.

410. Singer RB. Fecal occult blood testing and the incidence of colorectal cancer. *J Insur Med* 2002;34:89-91.

411. Chen K. [An applied study on the method of multi-factorial quantitative-risk assessment (MFQRA) for mass screening of colorectal cancer]. *Zhonghua Zhong Liu Za Zhi* 1993;15:37-40.

412. Kronborg O, Fenger C, Sondergaard O, Pedersen KM, Olsen J. Initial mass screening for colorectal cancer with fecal occult blood test: a prospective randomized study at Funen in Denmark. *Scand J Gastroenterol* 1987;22:677-86.

413. Slater PE, Fich A, Zimmerman J, Ever-Hadani P, Rachmilewitz D. Recruitment of subjects for fecal occult blood screening: a comparison of two methods in Jerusalem. *J Clin Gastroenterol* 1985;7:51-4.

414. Chen YK, Wise GR, Foliente RL. ColoCARE self-test versus Hemoccult II SENSA for fecal occult blood testing: response to 'friendly fire'. *Am J Gastroenterol* 1996;91:1672-73.

415. Kronborg O, Fenger C, Olsen J, Bech K, Sondergaard O. Repeated screening for colorectal cancer with fecal occult blood test: a prospective randomized study at Funen, Denmark. *Scand J Gastroenterol* 1989;24:599-606.

416. Slusser SO, Liberski SM, McGarrity TJ. Survival of patients diagnosed with colorectal cancer through a television-advertised screening program. *Am J Gastroenterol* 1996;91:1563-6.

417. Chen TH, Chiu YH, Luh DL, Yen MF, Wu HM, Chen LS, et al. Community-based multiple screening model: design, implementation, and analysis of 42,387 participants Taiwan community-based integrated screening group. *Cancer* 2004;100:1734-43.

418. Kronborg O, Fenger C, Worm J, Pedersen SA, Hem J, Bertelsen K, et al. Causes of death during the first 5 years of a randomized trial of mass screening for colorectal cancer with fecal occult blood test. *Scand J Gastroenterol* 1992;27:47-52.

419. Smith A, Young GP, Cole S, Morcom J, Chandler H, La Pointe L. A quantifiable fecal immunochemical test (FIT) for hemoglobin facilitates balancing sensitivity with specificity when screening for colorectal cancer. *Gastroenterology* 2004;126:A199.

420. Chiba M, Ueno F, Takahashi H, Arakawa S, Kawai H, Tahara M, et al. [Evaluation of fecal occult blood test, using latex agglutination inhibition method]. *Ther Res* 1990;11 Suppl 2:123-26.

421. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. [Randomized population study of screening for intestinal cancer with Hemoccult-II]. *Ugeskr Laeger* 1997;159:4977-81.

422. Sommer T, Kronborg O. Possible causes of a positive Haemoccult-II test in a population screening study for colorectal neoplasia. *Eur J Cancer Prev* 1996;5:181-7.

423. Ciatto S, Castiglione G. Role of double-contrast barium enema in colorectal cancer screening based on fecal occult blood. *Tumori* 2002;88:95-8.

424. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467-71.

425. Songster CL, Barrows GH, Jarrett DD. Immunochemical detection of fecal occult blood: the fecal smear punch-disc test: a new non-invasive screening test for colorectal cancer. *Cancer* 1980;45:1099-102.

426. Cohan C, Kadakia S. Prospective evaluation of patients with positive fecal occult blood test at digital rectal exam: is it worth it? *Gastroenterology* 1993;104:A393.

427. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Screening average risk persons with faecal occult blood tests: a randomised study with Hemoccult-II. *Gut* 1997;41:A8-A9.

428. Songster CL, Barrows GH, Jarrett DD. Immunochemical detection of human fecal occult blood. In: Winawer SJ, Schottenfeld D, Sherlock P, editors. *Colorectal cancer: prevention, epidemiology and screening*. New York: Raven Press; 1980. p. 193-204.

429. Cole SR, Sandford JJ, Cadd BA, Bennett J, Young GP, Bampton PA. Interval fecal occult blood testing in a colonoscopy based screening program. *Gastroenterology* 2001;120:A603.

430. Rasmussen M, Kronborg O. Upper gastrointestinal cancer in a population-based screening program with fecal occult blood test for colorectal cancer [summary for patients in J Fam Pract 2002 Jul;51(7):601]. *Scand J Gastroenterol* 2002;37:95-8.

431. Sontag SJ, Durczak C, Aranha GV, Chejfec G, Frederick W, Greenlee HB. Fecal occult blood screening for colorectal cancer in a Veterans Administration Hospital. *Am J Surg* 1983;145:89-94.

432. Cole SR, Young GP, Byrne D, Guy JR, Morcom J. Participation in screening for colorectal cancer based on a faecal occult blood test is improved by endorsement by the primary care practitioner. *J Med Screen* 2002;9:147-52.

433. Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol* 2004;39:846-51.

434. Souques M, Zummer K. [The Hemoccult II test: results of 16 years of screening tests at the Tumor Prevention Service of the City of Paris]. *Presse Med* 2000;29:983-6.

435. Cole S, Smith A, Bampton P, Sandford J, Morcom J, Young GP. Screening for colorectal cancer: direct comparison of a brush-sampling fecal immunochemical test for hemoglobin with Hemoccult. *Gastrointest Endosc* 2003;57:AB95.

436. Kruis W, Weinzierl M, Eisenberg J. [Endoscopic diagnoses in patients with positive Hemoccult-test: critical consideration and negative Hemoccult-test]. *Med Klin* 1979;74:1641-4.

437. St John DJB, Macrae FA, Caligiore P. Occult blood in colorectal cancer. *Gastroenterology* 1985;89:704-05.

438. Kruse JU, Jacobi D, Muller-Wieland K. [Results of a screening for colorectal carcinoma: a field-trial in the town Molln]. *Z Gastroenterol* 1982;20:273-5.

439. St.John DJB, McHutchison JG, Deacon M, Alexeyeff M, Young GP. Detection of colorectal pathology: comparison of hemoccult and hemoquant tests for occult blood. *Aust N Z J Med* 1988;18:404.

440. Colin R, le Grix A, Paillot B, Aubet JP, Cayron G, Robinson P, et al. [Detection polyps and cancers of the colon and the rectum: evaluation of the efficacy of fetal blood studies using guaiac-saturated plates]. *Nouv Presse Med* 1978;7:1204-5.

441. Kumanishi Y, Fujita M, Okuyama Y, Tsukamoto F, Watanabe T, Fujita Y, et al. [Mass screening for colorectal cander by a new economical RPHA method employed for detection of fecal occult blood from mixed extract of 3-day specimens]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1989;42:1051-57.

442. St.John DJB, Young GP, Cuthbertson AM, et al. Detection of colorectal neoplasia: comparison of guaiac, porphyrin and immunochemical tests for occult blood. *Gastroenterology* 1989;96:A492.

443. Conen D, Gallati H, Stalder GA. [Haemoccult and colorectal: a comparative prospective study on the detection of occult blood in the feces]. *Schweiz Med Wochenschr* 1981;111:706-8.

444. Kunz O, Siegel P. [Test for occult bleeding from the colon]. *Ther Ggw* 1976;115:1040-8.

445. St.John DJB, Sinatra MA, Young GP, Tilkeridis J, Alexeyeff MA. A further evaluation of the new immunochemical fecal occult blood test FlexSure OBT. *Gastroenterology* 1998;114:A684.

446. Cortes Ugalde F, Artal Moneva F, Garces Tapia A, Izcara Domingo J, Lacasa Serrano E, Zubiri Saenz F. [Colorectal cancer: detection using the guaiac test at a primary care center]. *Med Clin (Barc)* 1992;98:325-8.

447. Kurnick JE, Walley LB, Jacob HH, Nakayama L. Colorectal cancer detection in a community hospital screening program. *JAMA* 1980;243:2056-57.

448. Steinberg D, Steinberg JA. The Heme-Occult Program in Northwest Ohio. *Ohio State Med J* 1981;77:173-4.

449. Coughlin RJ, Friend WG. Dietary restrictions and fecal occult blood testing. *Am Fam Physician* 1987;35:118-20.

450. Kutter D. [Blood detection in feces without dietary restriction?]. *Dtsch Med Wochenschr* 1979;104:558.

451. Steinmetz J, Spyckerelle Y, Henny J, Giordanella JP, Emmanuelli J. [Screening for colorectal cancer: study of a population attending a public health clinic]. *Presse Med* 2001;30:1389-93.

452. Courtier R, Casamitjana M, Macia F, Panades A, Castells X, Gil MJ, et al. Participation in a colorectal cancer screening programme: influence of the method of contacting the target population. *Eur J Cancer Prev* 2002;11:209-13.

453. Lallemand RC, Vakil PA, Pearson P, Box V. Screening for asymptomatic bowel cancer in general practice. *Br Med J (Clin Res Ed)* 1984;288:31-3.

454. Steinmetz J, Spyckerelle Y, Giordanella JP. [Colorectal cancer: assessment of two-yearly screening of the population in health care examination centres]. *Presse Med* 2003;32:1496-9.

455. Crotta S, Castiglione G, Grazzini G, Valle F, Mosconi S, Rosset R. Feasibility study of colorectal cancer screening by immunochemical faecal occult blood testing: results in a northern Italian community. *Eur J Gastroenterol Hepatol* 2004;16:33-7.

456. Lamah M, Norris J, Caffarey SM, Broughton M, Marks CG. Effect of faecal occult blood testing on colorectal cancer mortality in the surveillance of subjects at moderate risk of colorectal neoplasia: a case-control study. *Int J Colorectal Dis* 2001;16:313-7.

457. Stelling HP, Maimon H, Smith RA, Bigley NJ, Mukherjee MD. New screening method for occult gastrointestinal bleeding: immunologic and guaiac slide tests. *J Fam Pract* 1984;19:757-61.

458. Crowley ML, Freeman LD, Mottet MD, Strong RM, Sweeney BF, Brower RA, et al. Sensitivity of guaiac-impregnated cards for the detection of colorectal neoplasia. *J Clin Gastroenterol* 1983;5:127-30.

459. LaPointe LC, Bruce RC, Roy M, Chandler H. Selecting for diagnostic colonoscopy by quantifiable fecal immunochemical tests. *Digestive Disease Week Abstracts and Itinerary Planner* 2003:A647.

460. Stelling HP, Maimon HN, Smith RA, Haddy RI, Markert RJ. A comparative study of fecal occult blood tests for early detection of gastrointestinal pathology. *Arch Intern Med* 1990;150:1001-5.

461. Cruz-Correa M, Schultz K, Jagannath S, Harris M, Kantsevoy S, Bedine M, et al. Comparative study of two fecal occult blood tests in patients undergoing colonoscopy: a validation study. *Gastroenterology* 2004;126:A195.

462. Larkin KK. Mass screening in colorectal cancer. *Aust N Z J Surg* 1980;50:467-9.

463. Sterchi JM. Screening for colorectal cancer. *South Med J* 1979;72:1144-6.

464. Cummings KM, Michalek A, Mettlin C, Mittelman A. Screening for colorectal cancer using the Hemoccult II stool guaiac slide test. *Cancer* 1984;53:2201-5.

465. Launoy G, Herbert C, Reaud JM, Thezee Y, Tichet J, Maurel J, et al. Haemoccult test properties according to type and number of positive slides in mass screening for colorectal cancer. *Br J Cancer* 1995;72:1043-6.

466. Stewart HL, Wiens E. Hemoccult test as a routine screening procedure for colorectal disease in the private clinic setting. *Can J Surg* 1979;22:572-4.

467. Cummings KM, Michalek A, Tidings J, Herrera L, Mettlin C. Results of a public screening program for colorectal cancer. *N Y State J Med* 1986;86:68-72.

468. Launoy G, Herbert C, Vallee JP, Desoubeaux N, Reaud JM, Ollivier V, et al. [Mass screening for colorectal cancer in France: experience in 165,000 people in the department of Calvados]. *Gastroenterol Clin Biol* 1996;20:228-36.

469. Stuart M, Killingback MJ, Sakker S, Failes DG, Frost GW, Mennie B. Hemoccult II test: routine screening procedure for colorectal neoplasm? *Med J Aust* 1981;1:629-31.

470. Daron PB, Goldman LI. Hemoccult screening in selected patients. *South Med J* 1981;74:676-8.

471. Lawson AH. The incidence of occult bleeding per rectum in a general practice in Scotland: a study using haemoccult. *Scott Med J* 1982;27:49-51.

472. Stuart M, Killingback MJ, Sakker S, Failes DG, Frost GW, Mennie B. The value of the hemoccult 11 test as a routine screening procedure for colorectal neoplasm. *Aust N Z J Med* 1981;11:227.

473. Desai SC, Sutherland GR. False-negative results of Haemoccult test. *Br Med J (Clin Res Ed)* 1981;283:1334.

474. Lazovich D, Weiss NS, Stevens NG, White E, McKnight B, Wagner EH. A case-control study to evaluate efficacy of screening for faecal occult blood. *J Med Screen* 1995;2:84-9.

475. Stuart M. Colorectal cancer screening. *Med J Aust* 1982;1:249.

476. Deyhle P, Nuesch HJ, Kobler E, Jenny S, Sauberli H. [The hemoccult test in the screening for colonic carcinoma]. *Schweiz Med Wochenschr* 1976;106:297.

477. Lee FI. Screening for colorectal cancer in a factory-based population with Fecatest. *Br J Cancer* 1983;48:843-7.

478. Suspiro A, Pinto A, Fidalgo P, Chagas C, Cravo M, NobreLeitao C, et al. Neoplasm spectrum detected by colonoscopy: comparison of a program based on fecal occult blood test vs family risk stratification. *Gastroenterology* 1997;112:A664.

479. Di Cicco M, Proietti M, Pelagalli M. [Screening of colorectal tumours by guaiac-test]. *Chir Gastroenterol* 1987;21:176-82.

480. Lee FI, Costello FT. Assessment of Fecatest and Haemoccult for faecal occult blood testing. *Br Med J (Clin Res Ed)* 1982;285:938.

481. Tada M. [Clinical study on the fecal occult blood test for the mass screening of colorectal cancer]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1983;36:119-24.

482. Di Vincenzo C, Salibra M, De Gaetano C, Filippone GF, Angotta C, Di Mauro S. [Detection of fecal occult blood in the screening of colorectal neoplasias]. *Chir Gastroenterol* 1989;23:136-40.

483. Leicester RJ, Lightfoot A, Millar J, Colin-Jones DG, Hunt RH. Accuracy and value of the Hemoccult test in symptomatic patients. *Br Med J (Clin Res Ed)* 1983;286:673-4.

484. Tadikonda L, Burke CA, Machicao V. Fecal occult blood testing for colorectal cancer screening: use the finger. *Am J Gastroenterol* 2000;95:2529.

485. Ostrow JD, Hansell JR, Mulvansy CA. Sensitivity and reproducibility of guaiac, hematest, and hemoccult test for fecal occult blood. *Ann Intern Med* 1972;76:860-61.

486. Leicester RJ, Colinjones DG, Hunt RH, Millar J, Leicester AI. Hemoccult testing in general practice for early diagnosis of colorectal cancer. *Gut* 1984;25:A561.

487. Takagi A, al. e. [Screening for colorectal cancer with immunological fecal occult blood test in clinical practice]. *Ther Res* 1993;14 Suppl 2:236-40.

488. Durst J, Neumann G, Schmidt K. [Occult blood in stool: a field trial in cancer screening]. *Dtsch Med Wochenschr* 1976;101:440-3.

489. Letsou G, Ballantyne GH, Zdon MJ, Zucker KA, Modlin IM. Screening for colorectal neoplasms: a comparison of the fecal occult blood test and endoscopic examination. *Dis Colon Rectum* 1987;30:839-43.

490. Takahashi H, Ide H, Shibayama Y, Ito T, Omata F, Ueno F, et al. Case finding of colorectal neoplasia with or without immunological fecal occult blood test. *Gastrointest Endosc* 1996;43:372.

491. Dvorak M, Kocna P, Vanickova Z. [Occult fecal blood loss--comparison of immunochemical and biochemical tests]. *Cas Lek Cesk* 2002;141:217-9.

492. Leu SY, Chou P, King TM, Mao IF. [Two-phase test of fecal occult blood screening for colorectal cancer]. *Zhonghua Yi Xue Za Zhi (Taipei)* 1990;46:265-70.

493. Takaki T, Kooriyama K, Ujiie K, Tsuchiya M, Hashiyada M. Detection of human hemoglobin with OC-hemocatch, a commercially available occult blood test. *Res Pract Forensic Med* 1995;38:101-04.

494. Dybdahl JH, Daae LN, Larsen S, Myren J. Occult faecal blood loss determined by a 51Cr method and chemical tests in patients referred for colonoscopy. *Scand J Gastroenterol* 1984;19:245-54.

495. Levenson DE, Steinberg WM. Hemeselect vs. hemoccult II in the diagnosis of colorectal neoplasms: a multicenter trial. *Gastroenterology* 1993;104:A420.

496. Takemasa I, Kikkawa N, Yasui M, Nishisho I, Fujitani K, Mishima H, et al. [Features of colorectal cancer with fecal-occult-blood tests: comparison with colorectal cancer with no screening]. *Gan To Kagaku Ryoho* 1998;25:1514-8.

497. Ebener B. Vergleich von haemoccult mit einem neuen immunologischen test: sensitivitat und spezifitat. *Z Gastroenterol* 1983;21:449.

498. Levin B, Hess K, Johnson C, Gray P, Maller A, Martin S. Screening for colorectal cancer: the impact of rehydration on the Hemoccult fecal occult blood test. *Gastroenterology* 1995;108:A496.

499. Takeshita T, Shiratori T, Kinoshita T, Ashizawa S. Immunological fecal occult blood testing (latex-agglutination method) for screening for colorectal cancer. *Nippon Daicho Komonbyo Gakkai Zasshi* 1985;38:780-83.

500. Ebling Z, Hadzic N. [The role of and suitability of the occult fecal blood test in a preventive program for colorectal carcinoma]. *Lijec Vjesn* 1989;111:432-6.

501. Levin B, Hess K, Johnson C. Screening for colorectal cancer: a comparison of 3 fecal occult blood tests. *Arch Intern Med* 1997;157:970-6.

502. Tarraga P, Garcia-Olmo D, Celada A, Garcia-Molinero M, Divison JA, Casado C. Colorectal cancer screening through detection of fecal occult blood in a controlled health zone. *Rev Esp Enferm Dig* 1999;91:335-44.

503. Eggertsen SC, Bergman JJ. A four-year experience with Hemoccult testing kits in a family medicine center. *J Fam Pract* 1983;16:1021-2, 24, 26.

504. Li S, Nie Z, Li N, Li J, Zhang P, Yang Z, et al. Colorectal cancer screening for the natural population of Beijing with sequential fecal occult blood test: a multicenter study. *Chin Med J (Engl)* 2003;116:200-2.

505. Tazi MA, Faivre J, Dassonville F, Lamour J, Milan C, Durand G. Participation in faecal occult blood screening for colorectal cancer in a well defined French population: results of five screening rounds from 1988 to 1996. *J Med Screen* 1997;4:147-51.

506. Eliakim R, Shabetai O, Rachmilewitz D. Screening for fecal occult blood in Israel: different approaches to recruitment. *J Clin Gastroenterol* 1988;10:173-5.

507. Li SR, Tian SL, Wu ZT, Han Y, Sheng JQ, Gao G, et al. [Application of sequential fecal occult blood test in consecutive screening of colorectal carcinoma for natural population]. *Shi Jie Hua Ren Xiao Hua Za Zhi* 2004;12:137-39.

508. Tazi MA, Faivre J, Lejeune C, Dassonville F, Benhamiche AM. [Informative value of Hemoccult test according to the number of positive slides in mass screening of colorectal cancer]. *Bull Cancer* 1998;85:1055-9.

509. Elliot MS, Levenstein JH, Wright JP. Faecal occult blood testing in the detection of colorectal cancer. *Br J Surg* 1984;71:785-6.

510. Lindholm E, Berglund B, Haglind E, Kewenter J. Factors associated with participation in screening for colorectal cancer with faecal occult blood testing. *Scand J Gastroenterol* 1995;30:171-6.

511. Tazi MA, Faivre J, Lejeune C, Benhamiche AM, Dassonville F. [Performance of the Hemoccult test in the screening of colorectal cancers and adenomas: results of 5 screening campaigns in Saone-et-Loire]. *Gastroenterol Clin Biol* 1999;23:475-80.

512. Elliot MS, Levenstein JH, Wright JP, Kottler RE. Early detection of colorectal cancer using faecal occult blood tests. *S Afr Med J* 1984;66:219-21.

513. Lipshutz GR, Katon RM, McCool MF, Mayer B, Smith FW, Duffy T, et al. Flexible sigmoidoscopy as a screening procedure for neoplasia of the colon. *Surg Gynecol Obstet* 1979;148:19-22.

514. Tazi MA, Faivre J, Lejeune C, Bolard P, Phelip JM, Benhamiche AM. Interval cancers in a community-based programme of colorectal cancer screening with faecal occult blood test. *Eur J Cancer Prev* 1999;8:131-5.

515. Escourrou J, Ribet A. A screening centre in Toulouse, France. *Int J Colorectal Dis* 1986;1:68-69.

516. Liu X, Zheng S, Chen K, et al. [Randomized controlled trial of sequence mass screening program for colorectal cancer]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2000;21:430-3.

517. Tellaroli JC, Gaucher P, Dornier R, et al. [Hemoccult, results concerning systematic check-up of the people over 45 working in the north-east medical zone of the SNCF]. *Annales Medicales de Nancy et de L'Est* 1981;20:1167-70.

518. Evelegh MJ, Marcon NE, Ryan ED, Ross CF, Gurney LA. Comparison of ColorectAlert to fecal occult blood testing and carcinoembryonic antigen for colorectal cancer screening. *Clin Chem* 2000;46:A161.

519. Lurie BB, Bull DM, Zamcheck N, Steward AM, Helms RA. Colon cancer: diagnostic and prognostic use of combined immunological testing. *J Clin Invest* 1974;53:48a.

520. Thomas WM, Pye G, Hardcastle JD, Mangham CM. Faecal occult blood screening for colorectal neoplasia: a randomized trial of three days or six days of tests. *Br J Surg* 1990;77:277-9.

521. Faivre J, Arveux P, Milan C, Durand G, Lamour J, Bedenne L. Participation in mass screening for colorectal cancer: results of screening and rescreening from the Burgundy study. *Eur J Cancer Prev* 1991;1:49-55.

522. Ma HF, Wang HM, Lin SY, Huang HI, Keng CL. The colorectal cancer screening program: VGHTC's early experience. *Formosan J Surg* 2003;36:209-13.

523. Thomas WM, Pye G, Hardcastle JD, Walker AR. Screening for colorectal carcinoma: an analysis of the sensitivity of haemoccult. *Br J Surg* 1992;79:833-5.

524. Faivre J, Tazi MA, Milan C, Lejeune C, Durand G, Lamour J. Controlled trial of faecal occult blood screening for colorectal cancer in Burgundy (France): results of the first 9 years. *Gastroenterology* 1999;116:A400.

525. Macafee DAL, Scholefield JH, Whynes DK. Distribution of colorectal cancers and adenomas in a screened population. *Gut* 2003;52 Suppl 1:A28.

526. Thomas W, White CM, Mah J, Geisser MS, Church TR, Mandel JS. Longitudinal compliance with annual screening for fecal occult blood Minnesota Colon Cancer Control Study. *Am J Epidemiol* 1995;142:176-82.

527. Faivre J, Tazi MA, El Mrini T, Lejeune C, Benhamiche AM, Dassonville F. Faecal occult blood screening and reduction of colorectal cancer mortality: a case-control study. *Br J Cancer* 1999;79:680-3.

528. Machicao VI, Burke C, Larive B. Comparison of fecal occult blood testing for colorectal cancer screening obtained by digital rectal examination versus spontaneously passed stools. *Gastroenterology* 1999;116:G2007.

529. Thurber LKB, Greenberg PD, Cello JP, Rockey DC. Utility of FlexSure(R) OBT, a new fecal occult blood test specific for human hemoglobin. *Gastrointest Endosc* 1996;43:329-29.

530. Mackett CW, Wilson CC, Brna TG, et al. Comparison of a galactose oxidase test to hemoccult in colorectal cancer screening. *Am J Gastroenterol* 1989;84:1190.

531. 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.

532. Faivre J, Dancourt V, LeJeune C, Murff HJ. Colorectal cancer mortality and biennial screening with fecal occult blood tests. *JCOM* 2004;11:498-99.

533. Van Maercke Y, Van Moer E, Pelckmans P, Pen J. [The Hemoccult(TM) test in a hospital population]. *Tijdschr Geneeskd* 1980;36:525-29.

534. Tin H, Lwin ZW, Desai DM, Shanon NJ. Flexible sigmoidoscopy in asymptomatic subjects with negative fecal occult blood tests. *Gastroenterology* 1993;104:A456.

535. Farrands PA, Griffiths RL, Britton DC. The Frome experiment: value of screening for colorectal cancer. *Lancet* 1981;1:1231-32.

536. Mahon SM. Fecal occult blood testing in a community cancer screening center. *Mo Nurse* 1994;63:19.

537. van Tongeren JH. [Population screening for colon and rectum cancer using the Hemoccult test]. *Ned Tijdschr Geneeskd* 1982;126:1967-9.

538. Fattah AS, Nakama H, Kamijo N, Fujimori K, Zhang B. Colorectal adenomatous polyps detected by immunochemical occult blood screening. *Hepatogastroenterology* 1998;45:712-6.

539. Makisumi K, Kinoshita T, Imakiire S, Makisumi J, Makisumi S, Ishizawa T, et al. The second-stage analysis on the results of mass screening for large bowel cancer. *Nippon Daicho Komonbyo Gakkai Zasshi* 1993;46:930-34.

540. Trojan J, Povse N, Schroder O, Stein J. A new immunological test strip device for the rapid, qualitative detection of faecal occult blood. *Z Gastroenterol* 2002;40:921-4.

541. Faure H, Exbrayat C, Garnier A, Dumas P, Winckel P, Bolla M. Influence of the 'directions for use' on positivity rates of the Hemoccult II test. *Eur J Gastroenterol Hepatol* 1998;10:1021-4.

542. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993;328:1365-71.

543. Tsukamoto Y, Okada M, Hirooka Y, Watanabe T, Goto H, Niwa Y, et al. A clinical study on the interval of examination to detect an early colorectal cancer. *Gastroenterology* 1997;112 (4 Suppl):A671.

544. Favennec L, Kapel N, Meillet D, Chochillon C, Gobert JG. Detection of occult blood in stools: comparison of three gaiac tests and a latex agglutination test. *Ann Biol Clin (Paris)* 1992;50:311-3.

545. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst* 1999;91:434-7.

546. Tsukioka S, Mita Y, Igarashi K, Hata K, Ho N, Ichii K. [Statistical evaluation of immunological fecal occult blood test results in patients with early colorectal cancer]. *Ther Res* 1995;16 Suppl 2:221-25.

547. Feifel G, Manner C, von Liebe S. Der haemoccult test ohne diatetische einschrankung. In: Goerttler K, editor. *Kolorektale krebsvorsorge*. Nurnberg: Wachholz; 1978. p. 110-15.

548. Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-7.

549. 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.

550. Feneyrou B, Bories P, Pomier-Layrargues G, Michel H. Discrepancy in results from three guaiacum resin tests. *Br Med J (Clin Res Ed)* 1982;284:235-6.

551. Mangla JC, Pereira M, Murphy J. Diagnosis of occult gastrointestinal lesions by stool guaiac testing in a geriatric hospital. *J Am Geriatr Soc* 1981;29:473-5.

552. Ferkl M, Kocna P, Fric P. [Comparison of immunochemical and biochemical methods for determination of occult fecal blood]. *Cas Lek Cesk* 1992;131:149-51.

553. Manus B, Bragelmann R, Armbrecht U, Stolte M, Stockbrugger RW. Screening for gastrointestinal neoplasia: efficacy and cost of two different approaches in a clinical rehabilitation centre. *Eur J Cancer Prev* 1996;5:49-55.

554. Uhlig K, Lampe J, Jacobasch KH, Wiedemann FH. Nachweis von okkultem blut im stuhl zur fruherkennung von kolon-rektum-tumoren. *Dtsch Gesundh Wes* 1978;33:2359-64.

555. Fernandez JL, Gallegos M, Brochero A, Arevalo C, Piccioni H, Gutierrez Galiana H. [Screening for colorectal cancer with an immunological fecal occult blood test]. *Acta Gastroenterol Latinoam* 1999;29:73-8.

556. Marchetto R, Volpato M, Ciccia B, Ghidoni C. [Asymptomatic colo-rectal cancer screening about risk cancer people with hemoccult slides tests]. *Chir Gastroenterol* 1989;23:297-301.

557. Uhlig K, Jacobasch KH, Lampe J. Haemoccult als screening zur fruherkennung von kolon-rektum-tumoren. *Dtsch Gesundh Wes* 1981;36:911-15.

558. Firouzi M, Khanna SC, Modares F, Gourgoutis G, Shah RM. Significance of hemoccult test obtained during rectal examination. *Gastroenterology* 1999;116:A57.

559. Marjoram J, Strachan R, Allan A, Allan E. Screening for colorectal cancer: a general-practice-based study. *Br J Gen Pract* 1996;46:283-86.

560. Ujszaszy L, Pronay G, Nagy G, Kovacs J, Libor J, Minik K. Screening for colorectal cancer in a Hungarian county. *Endoscopy* 1985;17:109-12.

561. Fischbach W, Grunenberg H. Detection of fecal occult blood in hospitalized patients, comparative evaluation of an immunochemical and a guaiac test. *Gastroenterology* 1996;110:A512.

562. Marks CG, Hardcastle JD. Occult blood screening for colorectal neoplasms using fecatwin sensitive and feca-eia. *Br J Surg* 1987;74:539.

563. Fleisher M, Schwartz MK, Winawer SJ. The false-negative hemoccult test. *Gastroenterology* 1977;72:782-4.

564. Marks RD, Hall G, Veerapalli R, Singh S. Fecal occult blood testing: does the stool collection method affect outcomes? *Gastroenterology* 1997;112:A29.

565. [Evaluation of mass screening for colorectal cancer with 'sequential fecal occult blood test' in an asymptomatic population Multicenter GI Research Group of Beijing Area of PLA]. *Zhonghua Zhong Liu Za Zhi* 1993;15:230-3.

566. Fleisher M, Schwartz MK, Winawer SJ. The use of fecal occult blood testing in detecting colorectal cancer. *Clin Chem* 1977;23:1157.

567. Matlock GA, Earnest DL. Effect of hydration on hemoccult II sensitivity. *Gastroenterology* 1979;76:1196.

568. Vandenbroucke-Van der Wielen A, Bourdon C, Delfosse H, Maisin H. [Interest of the Hemoccult test for the early diagnosis and the prevention of colo-rectal cancer]. *Louv Med* 1985;104:391-97.

569. Foliente RL, Wise GR, Collen MJ, Abdulian JD, Chen YK. Colocare self-test versus Hemoccult II Sensa for fecal occult blood testing. *Am J Gastroenterol* 1995;90:2160-3.

570. Maurer H, Hammer B. [Occult blood test in feces of hospitalized patients and out-patients: results of an own haemoccult study]. *Schweiz Rundsch Med Prax* 1982;71:1134-6.

571. Varro V. Early diagnosis of colorectal cancer: realities and perspectives. *Ann Gastroenterol Hepatol* 1982;18:370.

572. Ollivier JP, Foll Y, Rousseau M, Pauna B, Potier L, Laurent H, et al. Depistage des tumeurs colo-rectales par l'hemoccult. *Med Armees* 1981;9:117-21.

573. Mazzarello MG. [Occult blood in the feces for the early diagnosis of tumors of the digestive system]. *Minerva Med* 1990;81:687-90.

574. Verne J, Kettner J, Mant D, Farmer A, Mortenson N, Northover J. Self-administered faecal occult blood tests do not increase compliance with screening for colorectal cancer: results of a randomized controlled trial. *Eur J Cancer Prev* 1993;2:301-5.

575. Foschi D, Cavagna G, Beretta L, et al. [Study of the patients compliance with the 'hemoccult' as a test for asymptomatic colorectal cancer diagnosis]. *Riv It Colon Proctol* 1984;3:19-23.

576. McDonald C, Walls RS, Goulston KJ. Immunochemical test for fecal occult blood. *Aust N Z J Med* 1983;13:333.

577. Verne JE, Aubrey R, Love SB, Talbot IC, Northover JM. Population based randomized study of uptake and yield of screening by flexible sigmoidoscopy compared with screening by faecal occult blood testing. *BMJ* 1998;317:182-5.

578. Frame PS, Kowulich BA. Stool occult blood screening for colorectal cancer. *J Fam Pract* 1982;15:1071-5.

579. McGarrity TJ, Long PA, Peiffer LP, Converse JO, Kreig AF. Results of a television-advertised public screening program for colorectal cancer. *Arch Intern Med* 1989;149:140-4.

580. Villeneuve PJ, Coombs A. Screening for colorectal cancer using the fecal occult blood test: an actuarial assessment of the impact of a population-based screening program in Canada. *Int J Technol Assess Health Care* 2003;19:715-23.

581. Freedman JD, Mitchell CK. A simple strategy to improve patient adherence to outpatient fecal occult blood testing. *J Gen Intern Med* 1994;9:462-4.

582. McGarrity TJ, Long PA, Peiffer LP. Results of a repeat television-advertised mass screening program for colorectal cancer using fecal occult blood tests. *Am J Gastroenterol* 1990;85:266-70.

583. Wahrendorf J, Robra BP, Wiebelt H, Oberhausen R, Weiland M, Dhom G. Effectiveness of colorectal cancer screening: results from a population-based case-control evaluation in Saarland, Germany. *Eur J Cancer Prev* 1993;2:221-7.

584. Frommer DJ, Kapparis A. Immunological and hemoccult detection of fecal occult blood in patients with colorectal carcinomas and polyps. *Gut* 1984;25:A1171.

585. Mehler RB, Ostrow JD. Sensitivity of guaiac and unreliability of hematest method for detection of occult blood in feces. *Gastroenterology* 1969;56:1183.

586. Walter SD, Frommer DJ, Cook RJ. The estimation of sensitivity and specificity in colorectal cancer screening methods. *Cancer Detect Prev* 1991;15:465-9.

587. Frommer DJ, Kapparis A, Brown MK. Improved screening for colorectal cancer by immunological detection of occult blood. *Br Med J (Clin Res Ed)* 1988;296:1092-4.

588. Michalek A, Mettlin C, Bockstahler E. Hemoccult testing in a cancer screening clinic. *Prog Clin Biol Res* 1982;83:259-63.

589. Wanebo HJ, Fang WL, Mills AS, Zfass AM. Colorectal cancer: a blueprint for disease control through screening by primary care physicians. *Arch Surg* 1986;121:1347-52.

590. Fruhmorgen P. [Letter: Occult blood in feces]. *Dtsch Med Wochenschr* 1976;101:872-3.

591. Milkes DE, Gerson LB, Cheung R. Upper endoscopy (EGD) has a high diagnostic yield in asymptomatic, non-anemic patients with a positive fecal occult blood test (FOBT) compared to patients with a negative FOBT. *Gastrointest Endosc* 2003;57:AB116.

592. Warm K, Blazek Z, Weithofer G, Bloch R. [A modified guaiac test for the early detection of tumors of the intestinal tract]. *MMW Munch Med Wochenschr* 1977;119:285-8.

593. Fruhmorgen P, Demling L. Early detection of colorectal carcinoma with a modified guaiactest: a screening examination in 6000 humans. *Acta Gastroenterol Belg* 1978;41:682-7.

594. Miller MP, Stanley TV. Results of a mass screening program for colorectal cancer. *Arch Surg* 1988;123:63-5.

595. Webendorfer S, Messerer P, Eberle F, Zober A. [Precautions for intestinal cancer in the workplace: an initiative for secondary prevention in the BASF joint-stock company]. *Dtsch Med Wochenschr* 2004;129:239-43.

596. Fruhmorgen P, Demling L. Erste ergebnisse einer prospektiven feldstudie mit einem modifizierten guajak-test zum nachweis von okkultem blut im stuhl. In: Goerttler K, editor. *Kolorektale krebsvorsorge*. Nurnberg: Wachholz; 1978. p. 68-72.

597. Million R, Howarth J, Turnberg E, Turnberg LA. Faecal occult blood testing for colorectal cancer in general practice. *Practitioner* 1982;226:659-63.

598. Wechselberger F, Sfetsos G. Feldstudie an einem gesunden, arbeitsfahigen kollektiv von 40 bis 60 jahrigen arbeitnehmern zur fruherkennung des kolorektalen karzinoms mittels haemoccult-test. *Arbeitsmed Sozialmed Praventivmed* 1979;14:154-56.

599. Fruhmorgen P, Demling L. Early detection of colorectal cancer with modified guaiactest: a screening examination in 6000 humans. In: Winawer SJ, Schottenfeld D, Sherlock P, editors. *Colorectal cancer: prevention, epidemiology and screening*. New York: Raven Press; 1980. p. 311-15.

600. Mitsushima T, Nagatani K, Ikuma H, Inoue A, Ueno F. Sensitivity of immunological fecal occult blood testing in colorectal cancer, using total colonoscopy as the criterion standard. *Gastroenterology* 1994;106 (4 Suppl):A416.

601. Weiss W, Hanak H, Huber A. [Clinical value of rectal digital examination in early diagnosis of colorectal cancer]. *Wien Klin Wochenschr* 1977;89:654-60.

602. Fujita M, Nakano Y, Taguchi T, Sato M. A mass screening for colorectal cancer using fecal occult blood testing. *Nippon Daicho Komonbyo Gakkai Zasshi* 1981;34:306.

603. Miyoshi H, Oka M, Saitou O, Hirata I, Tanaka M, Sugi K, et al. The sensitivity of the newly developed immunological fecal occult blood test for colorectal neoplasia: comparison of the retrospective and prospective studies. *Gastroenterology* 1995;108:A509.

604. Weiss W, Samec HJ, Gulz W, Ortner H, Rudiger E, Neumayr A. [Clinical experience with occult blood test in 8784 patients]. *Wien Klin Wochenschr* 1981;93:291-6.

605. Fujita M, Taguchi T, Nakano Y, Oota J, Kimoto Y, Kumanishi Y, et al. [Mass screening for colorectal cancer by occult blood testing under restricted diet]. *Gan No Rinsho* 1984;30:925-32.

606. Moeller DD. Hemoccult screening: diagnosis of colorectal neoplasms. *J Kans Med Soc* 1983;84:10-11, 29.

607. Weller D, Thomas D, Hiller J, Woodward A, Edwards J. Screening for colorectal cancer using an immunochemical test for faecal occult blood: results of the first 2 years of a South Australian programme. *Aust N Z J Surg* 1994;64:464-9.

608. Fujita M, Nakano Y, Ohta J, Taguchi T. Mass screening for colorectal cancer by testing fecal occult blood. *Cancer* 1986;57:2241-5.

609. Monma T, Tukiyama S, Suehiro H, Maruoka E, Imataka K, Okano K. [Immunological detection of fecal occult blood-follow up study on patients with positive testing]. *Rinsho Byori* 1992;40:993-6.

610. Wells HJ, Guadagno P. Comparison of the sensitivity of a new fecal occult, blood test, coloscreen with hemoccult. *Clin Chem* 1980;26:1063-63.

611. Fujita M, Nakano Y, Ohta J, Kumanishi Y, Taguchi T. Mass screening for colorectal cancer by testing for occult blood under restricted diet and a questionnaire in Osaka. *Cancer Detect Prev* 1987;10:353-60.

612. Moran A, Hendrickse C, Jones AF, Neoptolemos JP. Loss of alpha(1)-protease inhibitor from colorectal cancer tissue and comparison with guaiac occult blood tests. *Br J Surg* 1994;81:1821.

613. Wexner SD, Brabbee GW, Wichern WA, Jr. Sensitivity of hemoccult testing in patients with colorectal carcinoma. *Dis Colon Rectum* 1984;27:775-6.

614. Fujiyoshi T, Takagi K, Fujiyoshi M, Hashimoto M, Tsuji Y, Fujimoto N, et al. Sigmoidoscopy and other tests for screening of colorectal cancer. *J Med Syst* 1993;17:157-62.

615. Depistage des tumeurs recto-coliques par l'hemoccult. *Nouv Presse Med* 1980;9:3189.

616. Wielinger H, Carstensen CA. Verbesserter test zum nachweis von okkultem blut im stuhl. *Munch Med Wschr* 1978;120:1095-96.

617. Gabrielsson N, Granqvist S, Nilsson B. Guaiac tests for detection of occult faecal blood loss in patients with endoscopically verified colonic polyps. *Scand J Gastroenterol* 1985;20:978-82.

618. Moriarty M, O'Donoghue D, Smith M, Gillatt A, Moss B. Results and analysis of a screening study for colorectal carcinoma in Ireland. *Ir J Med Sci* 1983;152:252.

619. Wilkes B, Bersani G, Mettlin C. Development of a community colorectal cancer program. In: *Oncology Nursing Society's Eighth Annual Congress*; 1983 May 18-21; San Diego, CA. Oncology Nursing Society; 1983. p. 66.

620. Gallati H. Detection of fecal occult blood: improvement of guaiac-test by a simple modification of technique. *Med Welt* 1978;29:1929-32.

621. Morimoto T, Hiwatashi N, Sato H, Miura M, Yamazaki H, Sugawara N, et al. [Experience of mass screening for colorectal cancer using immunological fecal occult blood test]. *Ther Res* 1990;11 Suppl 2:132-36.

622. 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.

623. Giacchero A, Munizzi F, Pugliese V, Aste H. [Hemoccult test sensitivity in the diagnosis of colo-rectal polyps]. *Minerva Dietol Gastroenterol* 1982;28:321-23.

624. Morris DW, Lee CS, Hansell JR, Ostrow JD. Validity of fecal occult blood tests in hospitalized patients. *Gastroenterology* 1974;66:857.

625. Willis FL, Fanning J. Digital rectal fecal occult blood screening during gynecologic examination. *Am J Obstet Gynecol* 2004;190:1422-3.

626. Gilbertsen VA, McHugh R, Schuman L, Williams SE. The earlier detection of colorectal cancers: a preliminary report of the results of the Occult Blood Study. *Cancer* 1980;45:2899-901.

627. Morris DM, Daron PB, Goldman LI. Hemoccult screening in selected patients: the hernia patient older than age fifty years. *Cancer* 1983;51:1261-3.

628. Winawer S, Weston E, Hajdu S, Edelman M, Sherlock P, Stearns M, et al. Sensitivity of diagnostic techniques in patients with positive fecal occult blood screening tests. *Gastrointest Endosc* 1978;24:213-13.

629. Gilbertsten VA, McHugh R, Schuman LM, Williams SE. Colon cancer control study: an interim report. In: Winawer SJ, Schottenfeld D, Sherlock P, editors. *Colorectal cancer: prevention, epidemiology and screening*. New York: Raven Press; 1980. p. 261-66.

630. Morris DM, Daron PB, Goldman LI. Screening for occult blood in selected patients: the potential for false-negatives. *Cancer* 1984;54:2272.

631. Winawer SJ, Miller DG, Schottenfeld D, Leidner SD, Sherlock P, Befler B, et al. Feasibility of fecal occult-blood testing for detection of colorectal neoplasia: debits and credits. *Cancer* 1977;40:2616-9.

632. Glober GA, Peskoe SM. Outpatient screening for gastrointestinal lesions using guaiac-impregnated slides. *Am J Dig Dis* 1974;19:399-403.

633. Morris JB, Stellato TA, Guy BB, Gordon NH, Berger NA. A critical analysis of the largest reported mass fecal occult blood screening program in the United States. *Am J Surg* 1991;161:101-5; discussion 05-6.

634. Winawer SJ, Miller DG, Dressler M, Schottenfeld D, Sherlock P, Edelman M, et al. Screening for early colorectal neoplasia with fecal occult blood testing. *Digestion* 1977;16:285-86.

635. Glober GA, Hundahl S, Stucke J, Choy M. Fecal occult blood testing for colorectal cancer in an ethnically diverse population. *West J Med* 1994;161:377-82.

636. Moss SM, Hardcastle JD, Coleman DA, Robinson MH, Rodrigues VC. Interval cancers in a randomized controlled trial of screening for colorectal cancer using a faecal occult blood test. *Int J Epidemiol* 1999;28:386-90.

637. Winawer SJ, Leidner SD, Miller DG, Schottenfeld D, Befler B, Kurtz RC, et al. Results of a screening program for detection of early colon cancer and polyps using fecal occult blood testing. *Gastroenterology* 1977;72:1150.

638. Gnauck R. Okkultes blut im stuhl als suchtest nach kolorektalem krebs und prakenzerosen polypen: eine felstudie bei 815 erwachsenen. *Z Gastroenterol* 1974;12:239-50.

639. Murakami R, Nakao M, Hosoi J, Tsukuma H, Yabuuchi T, Imanishi K, et al. [Comparison among various immunological fecal occult blood tests in mass screening for large bowel cancer with special reference to positive rate, positive predictive value and concordance of test results]. *Ther Res* 1989;10 Suppl 1:390-96.

640. Winawer S, Ginther M, Weston E, Reichlin B, Fleisher M, Cirone C, et al. Impact of modifications in fecal occult blood test on screening program for colorectal neoplasia. *Gastroenterology* 1978;74:1151.

641. Gnauck R. [Screening for colorectal cancer with the Haemoccult test]. *Leber Magen Darm* 1977;7:32-5.

642. Murakami R, et al. [Mass screening for colo-rectal cancer by combination of two kinds of immunological fecal occult blood tests: comparison of diagnostic validity between OC-Hemodia R Auto "Eiken" and Immunogold-Hem R]. *Ther Res* 1995;16 Suppl 2:216-20.

643. Winawer SJ, Miller DG, Schottenfeld D, Befler B, Bhargava D, Leidner SD, et al. Screening for colorectal cancer with fecal occult blood testing. *Front Gastrointest Res* 1979;5:28-34.

644. Gnauck R. [Clinical comparison of hemoFEC with Hemoccult II]. *Dtsch Med Wochenschr* 1978;103:1648-9.

645. Murata I, Yoshikawa I, Abe S, Nakano S, Tabaru A, Endoh M, et al. [Significance of a mass survey for colorectal cancer at the workplace]. *J UOEH* 1994;16:53-9.

646. Winawer SJ, Andrews M, Flehinger B, Sherlock P, Schottenfeld D, Miller DG. Progress report on controlled trial of fecal occult blood testing for the detection of colorectal neoplasia. *Cancer* 1980;45:2959-64.

647. Gnauck R. Screening for colorectal cancer with haemoccult. In: Nieburgs HE, editor. *Prevention and detection of cancer: Proceedings of the Third International Symposium on Detection and Prevention of Cancer, New York 1976, Part II, Vol. 1*. New York: Marcel Dekker; 1978. p. 397-402.

648. Myers RE, Turner B, Weinberg D, Hyslop T, Hauck WW, Brigham T, et al. Impact of a physician-oriented intervention on follow-up in colorectal cancer screening. *Prev Med* 2004;38:375-81.

649. Winawer SJ, Zauber AG, O'Brien MJ, Gottlieb LS, Sternberg SS, Stewart ET, et al. The National Polyp Study: design, methods, and characteristics of patients with newly diagnosed polyps. *Cancer* 1992;70:1236-45.

650. Gnauck R. [Clinical comparison of hemoFEC and hemoccult]. *Dtsch Med Wochenschr* 1979;104:1649-50.

651. Nagaoka S, Toyoshima H, Bandoh T, Oritu M. [Studies on colorectal cancer detected by fecal occult blood test]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1996;49:550-53.

652. Winawer SJ, Flehinger BJ, Schottenfeld D, Miller DG. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J Natl Cancer Inst* 1993;85:1311-8.

653. Gnauck R, Thomas L. [Haemoscreen in comparison with haemoccult as screening test for colorectal carcinoma]. *Dtsch Med Wochenschr* 1980;105:1643-6.

654. Nagasaka K, et al. [An analysis of false negative fecal occult blood test in the colorectal cancer screening program for apparently healthy population]. *Ther Res* 1993;14 Suppl 2:241-45.

655. Winchester DP, Shull JH, Scanlon EF, Murrell JV, Smeltzer C, Vrba P, et al. A mass screening program for colorectal cancer using chemical testing for occult blood in the stool. *Cancer* 1980;45:2955-58.

656. Gnauck R. Occult blood tests. *Lancet* 1980;1:822.

657. Nagasawa S, Shozushima M, Takahashi M, Akihama T, Chiba S, Kawata T, et al. [Comparative studies on screening methods of mass survey for colo-rectal cancer using hemoccult II test and RPHA after using hemoccult II]. *Ther Res* 1989;10 Suppl 1:381-86.

658. Winchester DP, Sylvester J, Maher ML. Risks and benefits of mass screening for colorectal neoplasia with the stool guaiac test. *CA Cancer J Clin* 1983;33:333-43.

659. Gnauck R. [Screening tests for colon cancer: a new comparison Haemoccult: hemoFEC and review of 9 years clinical experience with Haemoccult]. *Z Gastroenterol* 1982;20:84-92.

660. Nakajima T, Watanabe K, Watanabe T, Shibasaki K, Kamano K, Sakamoto K, et al. Effectiveness of fecal occult blood test for mass screening of colorectal cancer. *Int J Cancer* 2002:223-24.

661. Wise GR, Chen YK, Abdulian JD, Collen MJ. Colocare self-test versus hemoccult II sensa for fecal occult blood testing. *Gastroenterology* 1994;106 (4 Suppl):A451.

662. Gnauck R, Belzer U. Treffsicherheit bei wiederholtem haemoccult-screening nach darmkrebs. *Dtsch Arztebl* 1983;80:39-48.

663. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *Br J Cancer* 2003;89:23-8.

664. Withers JN, James WC. Colon cancer detection using guaiac screening. *Hawaii Med J* 1978;37:363-5.

665. Gnauck R. [Screening for cancer of the colon]. *Med Welt* 1983;34:1049-51.

666. Nakama H. A study on the efficacy of a screening program for colorectal cancer in a small Japanese village. *Clin Investig* 1994;72:117-21.

667. 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.

668. Hammes PH, Gnauck R, Hawle H. [Screening for colorectal neoplasia: comparison of Hemdetect and Haemoccult]. *Z Gastroenterol* 1989;27:611-3.

669. Nakama H, Kamijo N, Fujimori K, Horiuchi A, Fattah AS, Zhang B. Characteristics of colorectal cancer with false negative result on immunochemical faecal occult blood test. *J Med Screen* 1996;3:115-8.

670. 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.

671. Gomez JA, Diehl AK. Admission stool guaiac test: use and impact on patient management. *Am J Med* 1992;92:603-6.

672. Wrobleski C, Kadakia S, Kadakia A, Meier N. Prevalence of proximal colonic neoplasms in average risk asymptomatic patients over age 50 with negative fecal occult blood tests and flexible sigmoidoscopy. *Gastroenterology* 1993;104 (4 Suppl):A1067.

673. Goodman MJ. Mass screening for colorectal cancer: a negative report. *JAMA* 1977;237:2380.

674. Nakama H, Kamijo N, Fujimori K, Fattah AS, Zhang B. Relationship between fecal sampling times and sensitivity and specificity of immunochemical fecal occult blood tests for colorectal cancer: a comparative study. *Dis Colon Rectum* 1997;40:781-4.

675. Wu JCY, Leung W, Chan FKL, Lau JYW, Ching JYL, To KF, et al. Colonoscopy versus fecal occult blood test plus flexible sigmoidoscopy in the screening of colorectal neoplasms in average risk Chinese. *Gastroenterology* 2002;122:A481.

676. Goodman MJ. Screening for colorectal cancer. *JAMA* 1978;240:2733.

677. Nakama H, Kamijo N, Miyata K, Abdul Fattah AS, Zhang B, Uehara Y. Sensitivity and specificity of several immunochemical tests for colorectal cancer. *Hepatogastroenterology* 1998;45:1579-82.

678. Yamaguchi N, Watanabe Y, Tada M. [Evaluation of immunological fecal occult blood test]. *Rinsho Byori* 1988;36:751-8.

679. 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.

680. Nakama H, Kayano T, Katsuura T, Kamigaito T, Shimada S, Nishikawa N, et al. Comparison of predictive value for colorectal cancer in subjects with and without rectal bleeding. *Hepatogastroenterology* 1999;46:1730-2.

681. Yamamura M, et al. [Screening for colon malignancy with fecal occult blood testing]. *Ther Res* 1993;14 Suppl 2:336-42.

682. Goswitz JT. Mass Hemoccult screening for colon cancer in Manitowoc county. *Wis Med J* 1987;86:25-8.

683. Nakama H, Yamamoto M, Kamijo N, Li T, Wei N, Fattah AS, et al. Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. *Hepatogastroenterology* 1999;46:228-31.

684. Niv Y. Positive Hemoccult tests and colonoscopic results. *Ann Intern Med* 1986;105:470.

685. Goto A. [Immunological fecal occult blood testing with EIA for screening of colorectal cancer]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1988;41:945-49.

686. Nakama H, Zhang B, Zhang X, Fukazawa K. Age-related cancer detection rate and costs for one cancer detected in one screening by immunochemical fecal occult blood test. *Dis Colon Rectum* 2001;44:1696-9.

687. Yoshida Y, Saito H, Tsuchida S, Kakizaki R, Aisawa T, Munakata A. A simple sensitive immunological fecal occult blood test suitable for mass screening for colorectal cancer. *Gastroenterology* 1986;90:1699.

688. Zheng GM, Choi BC, Yu XR, Zou RB, Shao YW, Ma XY. Mass screening for rectal neoplasm in Jiashan County, China. *J Clin Epidemiol* 1991;44:1379-85.

689. Nakama H, Zhang B, Fukazawa K, Zhang X. Comparisons of cancer detection rate and costs of one cancer detected among different age-cohorts in immunochemical occult blood screening. *J Cancer Res Clin Oncol* 2001;127:439-43.

690. Yoshii Y, Kobayashi S, Ito Y, Kasugai T. Fecal occult blood testing with Shionogi slide for detection of colorectal cancer: evaluation of false-positive cases. *Nippon Daicho Komonbyo Gakkai Zasshi* 1980;33:298.

691. Grazzini G, Castiglione G, Isu A, Mantellini P, Rubeca T, Sani C, et al. Colorectal cancer screening by fecal occult blood testing: results of a population-based experience. *Tumori* 2000;86:384-8.

692. Nakama H, Zhang B, Fattah AS, Zhang X. Diagnostic yield of positive immunochemical occult-blood test by digital rectal examination: comparison between subjects with and without haemorrhoids. *Dig Liver Dis* 2001;33:390.

693. Yoshii Y, Kobayashi S, Kuroda T, Kasugai T. [Early carcinoma and adenoma of the large intestine: usefulness of fecal occult blood testing for detection and factors relating to bleeding]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1981;34:309.

694. Grazzini G, Castiglione G, Ciabattoni C, Franceschini F, Giorgi D, Gozzi S, et al. Colorectal cancer screening programme by faecal occult blood test in Tuscany: first round results. *Eur J Cancer Prev* 2004;13:19-26.

695. Nakama H, Zhang B. Diagnostic reliability of immunochemical faecal occult blood test for small colorectal flat adenomas. *Dig Liver Dis* 2001;33:301.

696. Yoshii Y, Kobayashi S, Matsuura A, Kasugai T. [Screening for colorectal cancer in clinical practice: evaluation of fecal occult blood testing in two successive days]. *Nippon Daicho Komonbyo Gakkai Zasshi* 1984;37:699-705.

697. Greegor DH. Diagnosis of large-bowel cancer in the asymptomatic patient. *JAMA* 1967;201:943-5.

698. Nakama H, Zhang B, Abdul Fattah AS, Kamijo N. Does stool collection method affect outcomes in immunochemical fecal occult blood testing? *Dis Colon Rectum* 2001;44:871-5.

699. Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K. Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *Am J Gastroenterol* 1995;90:1076-9.

700. Greegor DH. Detection of silent colon cancer in routine examination. *CA Cancer J Clin* 1969;19:330-7.

701. Ndjitoyap C, Paillot B. [Sensitivity and specificity of the Hemoccult test compared with fibrosigmoidoscopy in the detection of colorectal polyps]. *Gastroenterol Clin Biol* 1984;8:678-9.

702. Young GP, Deacon M, McHutchison JG, St John DJB. Evaluation of two immunochemical tests (ICT) for faecal occult blood. *Aust N Z J Med* 1986;16:618.

703. Greegor DH. Occult blood testing for detection of asymptomatic colon cancer. *Cancer* 1971;28:131-4.

704. Nichols S, Koch E, Lallemand RC, Heald RJ, Izzard L, Machin D, et al. Randomised trial of compliance with screening for colorectal cancer. *Br Med J (Clin Res Ed)* 1986;293:107-10.

705. Young GP, Sinatra MA, Alexeyeff MA, St John DJB. A preliminary evaluation of guaiac-based fecal occult blood tests with a unique test card format. *Gastroenterology* 1995;108 (4 Suppl):A557.

706. Greegor DH. A progress report: detection of colorectal cancer using guaiac slides. *CA Cancer J Clin* 1972;22:360-3.

707. Nicolopoulos N, Mantidis A, Bafaloucos D, Vranas P, Vasilakis J. The haemoccult test in a hospitalized population in Greece. *Hepatogastroenterology* 1980;27 Suppl:S99.

708. Young GP, St John DJB, Sinatra MA, Cole SC, Bielecki B, Bennett J, et al. Evaluation of a quantifiable immunochemical fecal occult blood test with simplified fecal sampling. *Gastroenterology* 2001;120:A599.

709. Greegor DH. Uber entstehung, durchfuhrung und folgen des modifizierten guajak-testes. In: Goerttler K, editor. *Kolorektale krebsvorsorge*. Nurnberg: Wachholz; 1978. p. 61-67.

710. Young G, Cole SR, Cadd B, Morcom J. Population participation in screening improves markedly using an immunochemical fecal occult blood test with simplified fecal sampling. *Gastroenterology* 2002;122:A484-A85.

711. Greegor DH. Detection of colon cancer in the asymptomatic patient. In: Nieburgs HE, editor. *Prevention and detection of cancer: Proceedings of the Third International Symposium on Detection and Prevention of Cancer, New York 1976, Part II, Vol. 2*. New York: Marcel Dekker; 1980. p. 2111-13.

712. Nishikawa A, Okuda T, Kubota I, Azuma H, Tanaka T, Koyasu T, et al. An evaluation of fecal occult blood screening in automated multiphasic health testing and services. *Jpn J Clin Oncol* 1987;17:107-12.

713. Young GP, St John DJ, Cole SR, Bielecki BE, Pizzey C, Sinatra MA, et al. Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. *J Med Screen* 2003;10:123-8.

714. 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.

715. Niv Y. Fecal occult blood test: the importance of proper evaluation. *J Clin Gastroenterol* 1990;12:393-5.

716. Zappa M, Castiglione G, Grazzini G, Falini P, Giorgi D, Paci E, et al. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the District of Florence, Italy. *Int J Cancer* 1997;73:208-10.

717. Gregorio DI, Lolachi P, Hansen H. Detecting colorectal cancer with a large scale fecal occult blood testing program. *Public Health Rep* 1992;107:331-5.

718. Niv Y. Does a risk questionnaire add anything to a colorectal screening project? Report of a 3-year screening experience. *J Clin Gastroenterol* 1992;15:33-6.

719. Zappa M, Castiglione G, Paci E, Grazzini G, Rubeca T, Turco P, et al. Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. *Int J Cancer* 2001;92:151-4.

720. Griffith CD, Turner DJ, Saunders JH. False-negative results of Hemoccult test in colorectal cancer. *Br Med J (Clin Res Ed)* 1981;283:472.

721. 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.

722. Zarchy TM, Ershoff D. Which clinical variables predict an abnormal double-contrast barium enema result? *Ann Intern Med* 1991;114:137-41.

723. Griffiths EK, Shapira DV. Risk factors in asymptomatic subjects screened for colorectal cancer. *Cancer Detect Prev* 1990;14:647-50.

724. Niv Y, Fraser GM. Screening for colorectal neoplastic lesions in Israeli kibbutz members using a combination of flexible sigmoidoscopy and fecal occult blood testing. *Gastrointest Endosc* 1996;43:369.

725. Zhang YL, Zhou DY, Lai ZS. Evaluation of immunological fecal occult blood test for colorectal tumor by specific antibody coated staphylococcal protein A coagglutination. *J Med Coll PLA* 1992;7:382-58.

726. Gysi B, Lang C, Affolter H. [Fecal occult blood: does a hemoglobin-specific tests improve the diagnosis of relevant colonic neoplasms?]. *Schweiz Med Wochenschr* 1991;121:988-90.

727. Niv Y, Lev-El M, Fraser G, Tamir A. Protective effect of fecal occult blood test screening for colorectal cancer: worse prognosis for screening refusers. *Gastroenterology* 1998;114:G2700.

728. Zhang B, Nakama H. Influence of irritable bowel syndrome to results of immunochemical fecal occult blood test. *GI Cancer* 2001;3:355-58.

729. Habba SF, Doyle JS. Colorectal cancer screening of asymptomatic patients in Ireland. *Ir J Med Sci* 1983;152:121-24.

730. Nobuo H, Tomizo M, Nobuyuki S, Hirofusa S, Takayoshi T. Characteristics of colorectal cancer with false-negative fecal occult blood in screening health care examination. *Stomach & Intestine* 1993;28:833-38.

731. Zheng S. [The screening model for early diagnosis of colorectal cancer in general population]. *Zhonghua Yi Xue Za Zhi* 1991;71:381-4, 28.

732. Habr-Gama A, Moreira H, Freitas IM, Gama-Rodrigues J, Penteado JF, Zeitune JM, et al. [Tracing of colorectal cancer by modified guaiaco test: a multicentric study in Brazil]. *GED Gastroenterol Endosc Dig* 1983;2:30-6.

733. Norfleet RG, Roberts RC. Hemoccult screening for colorectal neoplasms: report of a pilot project. *Wis Med J* 1979;78:25-6.

734. Zheng S, Chen K, Liu X, Ma X, Yu H, Yao K, et al. Cluster randomization trial of sequence mass screening for colorectal cancer. *Dis Colon Rectum* 2003;46:51-8.

735. Hakkinen I, Paasivuo R, Partanen P. Screening of colorectal tumours using an improved faecal occult blood test: quantitative aspects. *Gut* 1988;29:1194-7.

736. Norfleet RG, Roberts RC. Hemoccult screening for colorectal neoplasms: report of a mail-out project without dietary restriction in a prepaid health plan. *Wis Med J* 1983;82:23-6.

737. Zhou DY, Feng FC, Zhang YL. [A study on the complementary scheme of mass screening for colorectal cancer in an asymptomatic population]. *Zhonghua Nei Ke Za Zhi* 1994;33:367-9.

738. Hamajima E, Asai T, Okumura S, Yamaguchi H, Katou T, Yamamoto Y, et al. [Usefulness of combining a immunological fecal occult blood test (latex method) with a chemical test (guaiac method)]. *Gan No Rinsho* 1990;36:71-4.

739. Norfleet RG. Effect of diet on fecal occult blood testing in patients with colorectal polyps. *Dig Dis Sci* 1986;31:498-501.

740. Zolenko D, Cornette M, Oger A. [Screening for recto-colic neoplasms by the detection of occult blood in the stool: a study in the hospital milieu]. *Rev Med Liege* 1985;40:498-505.

741. Hammes PH, Gnauck R. [Does rehydration improve hemoccult screening for intestinal cancer?]. *Z Gastroenterol* 1985;23:676-80.

742. Nozaki R, Tanaka N, Tadakuma N, Moritai N, Takano M. Colorectal cancer screening using a combination of fecal occult blood testing and flexible sigmoidoscopy. *Early Colorectal Cancer* 2001;5:179-84.

743. Zoubek V, Zoubkova H. [Results of screening for colorectal carcinoma in the Bruntal District using the Haemoccult Test 1985-1986]. *Cas Lek Cesk* 1989;128:460-2.

744. Hammes PH, Gnauck R. [Does prolonging the test period improve screening for colorectal cancer?]. *Z Gastroenterol* 1987;25:607-11.

745. Odes HS, Rozen P, Ron E, Bass D, Bat L, Keren S, et al. Screening for colorectal neoplasia: a multicenter study in Israel. *Isr J Med Sci* 1992;28:21-8.

746. Zoubek V, Zoubkova H. [Experience with screening for colorectal carcinoma using the Haemoccult Test]. *Cesk Zdrav* 1989;37:117-21.

747. Han DS, Park JY, Lee OY, Sohn JH, Yoon BC, Choi HS, et al. Comparison of fecal occult blood tests for screening of colorectal neoplasia: a prospective study with total colonoscopy. *Gastroenterology* 1997;112:A574.

748. Odom TD, Miner PA, Fain J, Johnson N, Goldstein JL. Community-based FOBT screening program results in identification of significant colonic lesions. *Am J Gastroenterol* 2000;95:2545.

749. Zoubek V, Zoubkova H, Mruzek M. [Problems in the early diagnosis and treatment of colorectal carcinoma and adenoma in the aged]. *Vnitr Lek* 1990;36:998-1001.

750. Hardcastle JD, Balfour TW, Amar SS. Screening for symptomless colorectal cancer by testing for occult blood in general practice. *Lancet* 1980;1:791-3.

751. O'Donoghue DP, Moriarty M, Smith M, Gillatt A, Moss B. Fecal occult blood screening in the community: a feasibility study. *Ir J Med Sci* 1984;153:365.

752. Zoubek V, Zoubkova H. Results of screening for colorectal carcinoma in the District of Bruntal using the Haemoccult Test in 1985-1988. *Czech Med* 1990;13:52-7.

753. Hardcastle JD, Farrands PA, Balfour TW, Chamberlain J, Amar SS, Sheldon MG. Controlled trial of faecal occult blood testing in the detection of colorectal cancer. *Lancet* 1983;2:1-4.

754. Okamoto H, Takayama I, Ochiai M, Kitahara F, Yoda Y, Kobayashi K, et al. [Mass screening for colorectal cancer at a health care center in Yamanashi Prefecture: 5 Years experience]. *Endosc Forum Dig Dis* 1995;11:56-62.

755. Christensen F, Anker N, Mondrup M. Blood in faeces: a comparison of the sensitivity and reproductibility of five chemical methods. *Clin Chim Acta* 1974;57:23-27.

756. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. *J Natl Cancer Inst* 1997;89:1440-8.

757. Klaaborg KE, Madsen MS, Kronborg O. Acceptability in screening with Hemoccult-II for colorectal cancer. *Scand J Gastroenterol* 1986;21:24.

758. Lazovich D. *Evaluation of efficacy of fecal occult blood testing. Executive summary of dissertation*. Seattle, WA: Fred Hutchinson Cancer Research Center; 1994. Report No.: AHCPR-94-126.

759. Nivatvongs S, Gilbertsen VA, Goldberg SM, Williams SE. Distribution of large-bowel cancers detected by occult blood test in asymptomatic patients. *Dis Colon Rectum* 1982;25:420-1.

760. Ochiai K, Hanamura T, Funakoshi K, Uemura Y. Specific and sensitive immunological fecal-occult-blood test. *Clin Chem* 2002;48:A68.

761. Robinson MH, Hardcastle JD, Moss SM, Amar SS, Chamberlain JO, Armitage NC, et al. The risks of screening: data from the Nottingham randomised controlled trial of faecal occult blood screening for colorectal cancer. *Gut* 1999;45:588-92.

762. Robinson MH, Rodrigues VC, Hardcastle JD, Chamberlain JO, Mangham CM, Moss SM. Faecal occult blood screening for colorectal cancer at Nottingham: details of the verification process. *J Med Screen* 2000;7:97-8.

763. Sack EM, Bhattacharya I. Screening colonoscopy and Hemoccult (HII) testing: an evaluation of patient compliance with two colorectal cancer screening methodologies. *Gastroenterology* 1997;112 (4 Suppl):A649.

764. Stroehlein JR, Fairbanks VF, Go VL, Taylor WF, Thompson JH, Jr. Hemoccult stool tests: false-negative results due to storage of specimens. *Mayo Clin Proc* 1976;51:548-52.

765. Williams JA, Hunter R, Smith M, Coles ME, Hubert TW, Thomas DW. Evaluation of an immunological test for occult bleeding from colorectal neoplasia. *Aust N Z J Surg* 1982;52:617-21.

766. Young GP, Sinatra MA, St John DJ. Influence of delay in stool sampling on fecal occult blood test sensitivity. *Clin Chem* 1996;42:1107-8.

767. Allison JE, Feldman R. Cost benefits of hemoccult screening for colorectal carcinoma. *Dig Dis Sci* 1985;30:860-5.

768. Helm JF, Simpson KN, Sandler RS. Role of sigmoidoscopy and fecal occult blood testing (FOBT) in screening for colorectal cancer (CRC). *Gastroenterology* 1998;114:A18.

769. Robinson MH, Marks CG, Farrands PA, Whynes DK, Bostock K, Hardcastle JD. Is an immunological faecal occult blood test better than Haemoccult? A cost-benefit study. *Eur J Surg Oncol* 1995;21:261-4.

770. Aguiar EI, Eisenberg JM, Hill J, Engstrom P, Wolf T, Balshem A, et al. Economic assessment of colon cancer early detection through fecal occult blood testing. *Clin Res* 1992;40:A348.

771. Helm JF, Biddle AK, Simpson KN, Ransohoff DF, Sandler RS. A comparison of the effectiveness and economic impact of screening for colorectal cancer (CRC) by single sigmoidoscopy and fecal occult blood testing (FOBT). *Gastroenterology* 1999;116:A64.

772. Salkeld G, Young G, Irwig L, Haas M, Glasziou P. Cost-effectiveness analysis of screening by faecal occult blood testing for colorectal cancer in Australia. *Aust N Z J Public Health* 1996;20:138-43.

773. Aguiar R, Gimeno A, Parra-Blanco A, Nicolas D, Deniz D, Garcia M, et al. Cost-effectiveness analysis of colorectal cancer screening by immunochemical or biochemical faecal occult blood tests. *Gastroenterology* 2004;126:A344.

774. Joseph AM, Crowson TW, Rich EC. Cost effectiveness of hemoquant versus hemoccult for colon cancer screening. *Clin Res* 1987;35:349A.

775. Sorrentino D, Paduano R, Bernardis V, Piccolo A, Bartoli E. Colorectal cancer screening in Italy: feasibility and cost-effectiveness in a model area. *Eur J Gastroenterol Hepatol* 1999;11:655-60.

776. Applegate W, Spector MH. Cost-effectiveness of hemoccult screening for large bowel cancer. *Clin Res* 1979;27:30A.

777. Joseph AM, Crowson TW, Rich EC. Cost effectiveness of HemoQuant versus Hemoccult for colorectal cancer screening. *J Gen Intern Med* 1988;3:132-8.

778. Steele RJC, Gnauck R, Hrcka R, Kronborg O, Kuntz C, Moayyedi P, et al. Methods and economic considerations: Group 1 report. *Endoscopy* 2004;36:349-53.

779. Arveux P, Faivre J, Bedenne L, Durand G, Milan C. [Cost of a mass screening program for colorectal cancer using the hemoccult test]. *Gastroenterol Clin Biol* 1992;16:547-51.

780. Khandker RK, Dulski JD, Kilpatrick JB, Ellis RP, Mitchell JB, Baine WB. A decision model and cost-effectiveness analysis of colorectal cancer screening and surveillance guidelines for average-risk adults. *Int J Technol Assess Health Care* 2000;16:799-810.

781. Stone CA, Carter RC, Vos T, St John J. Colorectal cancer screening in Australia: an economic evaluation of a potential biennial screening program using faecal occult blood tests. *Aust N Z J Public Health* 2004;28:273-82.

782. US Congress, Office of Technology Assessment. *Cost-effectiveness of colorectal cancer screening in average-risk adults*. Washington DC: US Government Printing Office; 1995. Report No.: OTA-BP-H-146.

783. Kristein MM. The economics of screening for colorectal cancer. *Soc Sci Med* 1980;14:275-84.

784. Theuer CP, Wagner JL, Taylor TH, Brewster WR, Tran D, McLaren CE, et al. Racial and ethnic colorectal cancer patterns affect the cost-effectiveness of colorectal cancer screening in the United States. *Gastroenterology* 2001;120:848-56.

785. Bretthauer M, Gondal G, Larsen K, Carlsen E, Eide TJ, Grotmol T, et al. Design, organization and management of a controlled population screening study for detection of colorectal neoplasia: attendance rates in the NORCCAP study (Norwegian Colorectal Cancer Prevention). *Scand J Gastroenterol* 2002;37:568-73.

786. Lang CA, Ransohoff DF. Colorectal cancer screening: cost-effectiveness of the fecal occult blood test with and without rehydration. *Gastroenterology* 1994;106 (4 Suppl):A15.

787. Tsuji I, Fukao A, Shoji T, Kuwajima I, Sugawara N, Hisamichi S. Cost-effectiveness analysis of screening for colorectal cancer in Japan. *Tohoku J Exp Med* 1991;164:269-78.

788. Brown K, Burrows C. The sixth stool guaiac test: $47 million that never was. *J Health Econ* 1990;9:429-45.

789. Lejeune C, Arveux P, Dancourt V, Fagnani F, Bonithon-Kopp C, Faivre J. A simulation model for evaluating the medical and economic outcomes of screening strategies for colorectal cancer. *Eur J Cancer Prev* 2003;12:77-84.

790. Vijan S, Hwang EW, Hofer TP, Hayward RA. Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. *Am J Med* 2001;111:593-601.

791. Byers T, Gorsky R. Estimates of costs and effects of screening for colorectal cancer in the United States. *Cancer* 1992;70:1288-95.

792. Lejeune C, Dancourt V, Arveux P, Bonithon-Kopp C, Faivre J. Analyse cout-efficacite du depistage du cancer colo-rectal par le test hemoccultr en France. *Gastroenterol Clin Biol* 2003;27:A104.

793. Vilan S, Hwang E, Hofer TP, Hayward RA. Screening strategies for colon cancer: flexible sigmoidoscopy and fecal occult-blood testing versus colonoscopic screening. *J Investig Med* 1997;45:317A.

794. Canadian Coordinating Office for Health Technology Assessment. *Economic evaluation of population-based screening for colorectal cancer. Pre-assessment No. 6*. Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment; 2002.

795. Wagner JL, Herdman RC, Wadhwa S. Cost effectiveness of colorectal cancer screening in the elderly. *Ann Intern Med* 1991;115:807-17.

796. Chang JT, Lawrence WF, Mandelblatt JS. Colorectal cancer screening with fecal occult blood testing in the elderly. *J Gen Intern Med* 1999;14 Suppl 2:91.

797. Lejeune C, Arveux P, Dancourt V, Bejean S, Bonithon-Kopp C, Faivre J. Cost-effectiveness analysis of fecal occult blood screening for colorectal cancer. *Int J Technol Assess Health Care* 2004;20:434-39.

798. Wagner JL, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average-risk adults. In: Young GP, Rozen P, Levin B, editors. *Prevention and early detection of colorectal cancer*. London: WB Sanders; 1996. p. 321-41.

799. Cornell RG. Sequence length of repeated screening tests. *J Chron Dis* 1978;31:539-46.

800. Lieberman D. Cost-effectiveness of colon cancer screening. *Am J Gastroenterol* 1991;86:1789-94.

801. Walker A, Whynes DK, Chamberlain JO, Hardcastle JD. The cost of screening for colorectal cancer. *J Epidemiol Community Health* 1991;45:220-4.

802. Delco F, Sonnenberg A, Inadomi JM. Screening for colorectal cancer: colonoscopy is more cost-effective than fecal occult blood test. *Gastroenterology* 1999;116:A394.

803. Lieberman D. Cost-effectiveness of colon cancer screening: fecal occult blood test vs colonoscopy. *Gastroenterology* 1995;108:A497.

804. Walker AR, Whynes DK, Hardcastle JD. Rehydration of guaiac-based faecal occult blood tests in mass screening for colorectal cancer: an economic perspective. *Scand J Gastroenterol* 1991;26:215-8.

805. Eddy D. Cost-effectiveness of colorectal cancer screening. In: Levin B, Riddell RH, editors. *Frontiers in gastrointestinal cancer*. New York: Elsevier; 1984. p. 203-19.

806. Lieberman D. Impact of combined flexible sigmoidoscopy and fecal occult blood-test in colon-cancer screening: a cost-effectiveness model. *Gastroenterology* 1995;108:A498.

807. Walker A. *An economic evaluation of mass population screening for colorectal cancer using a faecal occult blood test [dissertation]* [PhD]. Nottingham: Nottingham University, 1993.

808. Eickhoff A, Riemann JF. [Health economic aspects colorectal cancer: prevention, treatment and follow-up: what is the most cost-effective approach?]. *Gesundh ökon Qual manag* 2002;7:232-40.

809. Lieberman DA. Cost-effectiveness model for colon cancer screening. *Gastroenterology* 1995;109:1781-90.

810. Weller D, Moss J, Hiller J, Thomas D, Edwards J. Screening for colorectal cancer: what are the costs? *Int J Technol Assess Health Care* 1995;11:26-39.

811. Feldman R, Allison JE. Cost evaluation of hemoccult stool testing to detect asymptomatic colorectal cancer. *Gastroenterology* 1981;80:1147.

812. McGrath JS, Gregor JC, Ponich TP. How much does it cost to find a patient with a significant polyp? *Gastroenterology* 2001;120:A602.

813. Whynes DK, Walker AR, Hardcastle JD. Effect of subject age on costs of screening for colorectal cancer. *J Epidemiol Community Health* 1992;46:577-81.

814. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA* 2000;284:1954-61.

815. McGrath JS, Ponich TP, Gregor JC. Screening for colorectal cancer: the cost to find an advanced adenoma. *Am J Gastroenterol* 2002;97:2902-7.

816. Whynes DK, Walker AR, Chamberlain JO, Hardcastle JD. Screening and the costs of treating colorectal cancer. *Br J Cancer* 1993;68:965-8.

817. Fric P, Zoubek V, Dvorakova H, Roth Z. [Costs and benefits of screening for colorectal tumors using the Hemoccult test in asymptomatic individuals 45-60 years of age]. *Cas Lek Cesk* 1991;130:370-3.

818. McMahon PM, Bosch JL, Gleason S, Halpern EF, Lester JS, Gazelle GS. Cost-effectiveness of colorectal cancer screening. *Radiology* 2001;219:44-50.

819. Whynes DK, Walker AR, Neilson AR. Cost-effectiveness of faecal occult blood screening for colorectal cancer: results of the Nottingham trial. *Eur J Cancer* 1997;33:OP30.

820. Fric P, Zavoral M, Dvorakova H, Zoubek V, Roth Z. An adapted program of colorectal cancer screening: 7 years experience and cost-benefit analysis. *Hepatogastroenterology* 1994;41:413-6.

821. Nakama H, Zhang B, Fattah AS. A cost-effective analysis of the optimum number of stool specimens collected for immunochemical occult blood screening for colorectal cancer. *Eur J Cancer* 2000;36:647-50.

822. Whynes DK, Neilson AR, Walker AR, Hardcastle JD. Faecal occult blood screening for colorectal cancer: is it cost-effective? *Health Econ* 1998;7:21-9.

823. Gow J. Costs of screening for colorectal cancer: an Australian programme. *Health Econ* 1999;8:531-40.

824. Nakama H, Zhang B, Zhang X. Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. *Eur J Cancer* 2001;37:398-401.

825. Whynes DK. Cost-effectiveness of faecal occult blood screening for colorectal cancer: results of the Nottingham trial. *Crit Rev Oncol Hematol* 1999;32:155-65.

826. Gyrd-Hansen D. Fecal occult blood tests: a cost-effectiveness analysis. *Int J Technol Assess Health Care* 1998;14:290-301.

827. Neilson AR, Whynes DK. Cost-effectiveness of screening for colorectal cancer: a simulation model. *IMA J Math Appl Med Biol* 1995;12:355-67.

828. Whynes DK. Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial. *J Med Screen* 2004;11:11-15.

829. Gyrd-Hansen D, Sogaard J, Kronborg O. Colorectal cancer screening: efficiency and effectiveness. *Health Econ* 1998;7:9-20.

830. Neuhauser D, Lweicki AM. What do we gain from the sixth stool guaiac? *N Engl J Med* 1975;293:226-8.

831. Yamamoto M, Nakama H. Cost-effectiveness analysis of immunochemical occult blood screening for colorectal cancer among three fecal sampling methods. *Hepatogastroenterology* 2000;47:396-9.

832. Helm JF, Russo MW, Simpson KN, Ransohoff DF, Sandler RS. Screening for colorectal cancer (CRC) by fecal occult blood testing (FOBT) is cost-effective, but is it affordable? *Gastroenterology* 1997;112:A18.

833. O'Leary BA, Olynyk JK, Neville AM, Platell CF. Cost-effectiveness of colorectal cancer screening: comparison of community-based flexible sigmoidoscopy with fecal occult blood testing and colonoscopy. *J Gastroenterol Hepatol* 2004;19:38-47.

834. Yoshinaga M, Motomura S, Ohtani A. Evaluation of the effectiveness of three screening methods for colorectal neoplasma. *Gastroenterology* 1997;112 (4 Suppl):A687.

835. Helm JF, Quade D, Russo MW, Simpson KN, Ransohoff DF, Sandler RS. What do we gain by screening for colorectal cancer (CRC) with six tests for fecal occult blood, and at what cost? *Gastroenterology* 1997;112 (4 Suppl):A576.

836. Parson RE, Baker JT. Cost-effectiveness of early detection and prevention of colorectal cancer by screening with fecal occult blood tests. *Value Health* 2000;3:130.

837. Zauber AG, Van Ballegooijen M, Brown M, Boer R, Habbema D, Loeve F, et al. Impact of immunochemical versus guaiac fecal occult blood tests (FOBT) for life years gained (LYG) and cost. *Gastroenterology* 2003;124:A5.

APPENDIX A: ADVISORY PANEL MEMBERS

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APPENDIX B: FOBT DEVICES

Table 19: Guaiac FOBT devices

UK name	Brand name	Alternative names	Name used in review	Manufacturer	UK distributor
ColoScreen	ColoScreen	ColoScreen-ES	**N/A**	Helena Laboratories UK Headquarters Colima Avenue Sunderland Enterprise Park Sunderland, Tyne & Wear SR5 3XB, U.K.	POCT distributor GTA (UK) Limited 34 Nottingham South Industrial Estate Ruddington Lane, Wilford Nottingham, NG11-7EP
Haemoccult	Haemoccult	Hemoccult HemeOccult Haemoccult II Hemoccult II HemeOccult II	**Haemoccult**	Beckman Coulter Oakley Court Kingsmead Business Park London Road High Wycombe Buckinghamshire HP11 1JU	Analytical technologies http://www.analyticaltechnologies.co.uk subsidiary of YSI Inc POCT Woodfield House, Forfar Road, Arbroath, Angus, DD11 3RA
Haemoccult Sensa	Haemoccult Sensa	Hemoccult Sensa Elite	**Haemoccult Sensa**	Beckman Coulter Oakley Court Kingsmead Business Park London Road High Wycombe Buckinghamshire HP11 1JU	Analytical technologies http://www.analyticaltechnologies.co.uk subsidiary of YSI Inc POCT Woodfield House, Forfar Road, Arbroath, Angus, DD11 3RA
Hema-screen	Hema-screen	Used as the foundation for Colon Alert in the US	**N/A**	Immunostics 3505 Sunset Ave, Ocean, NJ 07712 US	Alpha Laboratories Limited 40 Parham Drive Eastleigh Hampshire SO50 4NU
Hemdetect	Hemdetect	None known	**N/A**	Unknown	Autogen Bioclear UK Ltd Holly Ditch Farm, Mile Elm, Calne, Wiltshire, SN11 0PY

UK name	Brand name	Alternative names	Name used in review	Manufacturer	UK distributor
Hemo-FEC	Hemo-FEC	None known	**N/A**	Unknown	Roche Diagnostics UK & Ireland http://www.roche-diagnostics.co.uk/index.html
Occutest	Mast-Occutest	None known	**N/A**	Unknown	Mast Group Ltd. MAST House, Derby Road, Bootle, Merseyside, L20 1EA
None	KryptoHaem	Krypto Haem-SSWR Krypto Haem-SSW Krypto Häm	**KryptoHaem**	Unknown	None known
None	Shionogi B	None known	**Shionogi B**	Shionogi Pharmaceutical Co, Japan	None known

Table 20: Immunochemical FOBT devices

UK name	Brand name	Alternative names	Name used in review	Manufacturers	UK distributors
Check4-Haemoglobin	Quadratech-Check4	Check4-Haem	**N/A**	Veda Lab Parc d'Activités du Londeau BP 181 - 61006 Alençon cedex France	Quadratech Ltd PO Box 167 Epsom Surrey KT18 7YL
Hema-screen Specific	Hema-screen Specific	None known	**N/A**	Alpha Laboratories Limited 40 Parham Drive Eastleigh Hampshire SO50 4NU	Alpha Laboratories Limited 40 Parham Drive Eastleigh Hampshire SO50 4NU
RapydTest	RapydTest	Ease-A-cult	**N/A**	DiaSys Europe Ltd Unit 5 Sapphire Centre, Fishponds Road, Wokingham, Berkshire, RG41 2QL	DiaSys Europe Ltd Unit 5 Sapphire Centre, Fishponds Road, Wokingham, Berkshire, RG41 2QL

UK name	Brand name	Alternative names	Name used in review	Manufacturers	UK distributors
	OC Light	OC Hemocatch OC Hemodia Eiken OC Hemodia-Eiken	**OC Light**	Nagase www.nagase.com	None known
	LA Hemochaser	LA Hemo Chaser	**LA Hemochaser**	Mizuho Medy co. Ltd Tokyo, Japan	None known
	HB latex	Stick HB latex	**HB latex**	Operon Camino del Plano 19.50410-Cuarte de Huerva (Zaragoza), Spain	None known
	SPA test	None known	**SPA test**	Unkown	None known
	Ouchterlony	None known	**Ouchterlony**	Unkown	None known
	MonoHaem	None	**MonoHaem**	Nihon Pharmaceuticals Tokyo, Japan	None known
	Hemo-EIA	None known	**Hemo-EIA**	Unkown	None known
	Stick EIA	None known	**Stick EIA**	Unkown	None known
	Checkmate hemo	EIA - Checkmate hemo	**Checkmate hemo**	Unkown	None known
	Feca-EIA	Fecatwin SST Fecatwin EIA	**Feca-EIA**	Labsystems Co Helsinki, Finland	Henleys Medical Brownfields, Welwyn Garden City Herts AL7 1AN
	Iatro Hemcheck	None known	**Iatro Hemcheck**	Unkown	None known

APPENDIX C: DETAILED SEARCH STRATEGIES

This appendix presents the detailed searches carried out to inform the review.

MEDLINE: Ovid web interface. 1966-2004/Jul week 4. 30th July 2004.

The MEDLINE search covered the date range 1966 to July 2004. The search was carried out on 30th July 2004 and identified 1724 records.

1. exp Colorectal Neoplasms/
2. exp Cecal Neoplasms/
3. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
4. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
5. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
6. ((sigmoid$ or rectosigmoi$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
7. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
8. (large bowel$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
9. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
10. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
11. (hepatic flexur$ adj (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
12. (splenic flexur$ adj (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
13. or/1-12
14. Occult Blood/
15. occult blood.ti,ab.
16. occult bleed$.ti,ab.
17. (blood$ adj3 (stool$ or fece$ or faece$)).ti,ab.
18. (hidden adj3 blood$).ti,ab.
19. fecal occult.ti,ab.
20. faecal occult.ti,ab.
21. or/14-20
22. 13 or 21
23. Reagent Kits, Diagnostic/
24. (fecal occult blood adj (test$ or measure$)).ti,ab.
25. (faecal occult blood adj (test$ or measure$)).ti,ab.
26. (fecal occult blood adj (screen$ or exam$)).ti,ab.
27. (faecal occult blood adj (screen$ or exam$)).ti,ab.
28. (stool occult blood adj (test$ or measure$ or screen$ or exam$)).ti,ab.
29. (FOBT or FOB).ti,ab.
30. ((stool$ or fece$ or faece$) adj3 (card or cards)).ti,ab.
31. ((disposable or flushable) adj3 (reagent$ or pad or pads or test$ or kit or kits)).ti,ab.
32. GUAIAC/
33. (guaiac or guiac).ti,ab.
34. (haemoccult or haemoccult).ti,ab.
35. haemoccultsensa.ti,ab.
36. hemocare.ti,ab.
37. seracult.ti,ab.
38. coloscreen.ti,ab.
39. (hemascreen or hema screen).ti,ab.

40. (hemachek or hema chek).ti,ab.
41. (hemocheck or hemochek or hemo check or hemo chek).ti,ab.
42. (hemawipe or hema wipe).ti,ab.
43. monohaem.ti,ab.
44. (hemofec or hemofecia).ti,ab.
45. (fecatest or fecatwin).ti,ab.
46. (immunochemical$ adj3 (test$ or screen$ or diagn$)).ti,ab.
47. (immunologic$ adj3 (test$ or screen$ or diagn$)).ti,ab.
48. colocare.ti,ab.
49. hemeselect.ti,ab.
50. immudia.ti,ab.
51. flexsure.ti,ab.
52. (ez detect$ or e z detect$).ti,ab.
53. immocare.ti,ab.
54. (!nform or !nsure).ti,ab.
55. (hemchek or hem chek).ti,ab.
56. (magstream or HemSP or bayer detect).ti,ab.
57. hemochaser.ti,ab.
58. hemodia.ti,ab.
59. (bm-test or bmtest or colon albumin).ti,ab.
60. or/23-59
61. 22 and 60
62. Animal/
63. Human/
64. 62 not (62 and 63)
65. 61 not 64

EMBASE: Ovid web interface. 1980-2004/week 30. 30th July 2004.

The EMBASE search covered the date range 1980 to July 2004. The search was carried out on 30th July 2004 and identified 1292 records.

1. exp large intestine tumor/
2. exp large intestine cancer/
3. exp rectum cancer/
4. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
5. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
6. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
7. ((sigmoid$ or rectosigmoi$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
8. ((cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
9. (large bowel$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
10. (large intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
11. (lower intestin$ adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
12. (hepatic flexur$ adj (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
13. (splenic flexur$ adj (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).ti,ab.
14. or/1-13
15. occult blood/
16. occult blood.ti,ab.
17. occult bleed$.ti,ab.

18. (blood$ adj3 (stool$ or fece$ or faece$)).ti,ab.
19. hidden blood$.ti,ab.
20. fecal occult.ti,ab.
21. faecal occult.ti,ab.
22. or/15-21
23. 14 or 22
24. occult blood test/
25. (fecal occult blood adj (test$ or measure$)).ti,ab.
26. (faecal occult blood adj (test$ or measure$)).ti,ab.
27. (fecal occult blood adj (screen$ or exam$)).ti,ab.
28. (faecal occult blood adj (screen$ or exam$)).ti,ab.
29. (stool occult blood adj (test$ or measure$ or screen$ or exam$)).ti,ab.
30. (FOBT or FOB).ti,ab.
31. ((stool$ or fece$ or faece$) adj3 (card or cards)).ti,ab.
32. ((disposable or flushable) adj3 (reagent$ or pad or pads or test$ or kit or kits)).ti,ab.
33. Guaiac/
34. (guaiac or guiac).ti,ab.
35. (haemoccult or haemoccult).ti,ab.
36. haemoccultsensa.ti,ab.
37. hemocare.ti,ab.
38. seracult.ti,ab.
39. coloscreen.ti,ab.
40. (hemascreen or hema screen).ti,ab.
41. (hemachek or hema chek).ti,ab.
42. (hemocheck or hemochek or hemo check or hemo chek).ti,ab.
43. (hemawipe or hema wipe).ti,ab.
44. monohaem.ti,ab.
45. (hemofec or hemofecia).ti,ab.
46. (fecatest or fecatwin).ti,ab.
47. (immunochemical$ adj3 (test$ or screen$ or diagn$)).ti,ab.
48. (immunologic$ adj3 (test$ or screen$ or diagn$)).ti,ab.
49. colocare.ti,ab.
50. hemeselect.ti,ab.
51. immudia.ti,ab.
52. flexsure.ti,ab.
53. (ez detect$ or e z detect$).ti,ab.
54. immocare.ti,ab.
55. (!nform or !nsure).ti,ab.
56. (hemchek or hem chek).ti,ab.
57. (magstream or HemSP or bayer detect).ti,ab.
58. hemochaser.ti,ab.
59. hemodia.ti,ab.
60. (bm-test or bmtest or colon albumin).ti,ab.
61. or/24-60
62. 23 and 61
63. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
64. exp animal/
65. Nonhuman/
66. exp human/
67. 63 or 64 or 65
68. 67 not (67 and 66)
69. 62 not 68

BIOSIS: Dialog. 1969-2004/07. 30th July 2004.

The BIOSIS search covered the date range 1969 to July 2004. The search was carried out on 30th July 2004 and identified 899 records.

s (colorect? or colo rect?)(3N)(cancer? or neoplasm? or oncology? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (colon or colonic)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (rectal? or rectum?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (sigmoid? or rectosigmoi?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)bowel?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (lower(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s s1:s8
s occult(W)blood
s occult(W)bleed?
s blood?(3N)(stool? or fece? or faece?)
s (hidden(3N)blood?)
s fecal(W)occult or faecal(W)occult
s s10:s14
s s9 or s15
s fecal(W)occult(W)blood(W)(test? or measure?)
s faecal(W)occult(W)blood(W)(test? or measure?)
s fecal(W)occult(W)blood(W)(screen? or exam?)
s faecal(W)occult(W)blood(W)(screen? or exam?)
s stool(W)occult(W)blood(W)(test? or measure? or screen? or exam?)
s FOBT or FOB
s (stool? or fece? or faece?)(3N)(card or cards)
s (disposable or flushable)(3N)(reagent? or pad or pads or test? or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(W)chek or hemawipe or hema(W)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical?(3N)(test? or screen? or diagn?)
s immunologic?(3N)(test? or screen? or diagn?)
s colocare or hemeselect or immudia or flexsure or ez(W)detect? or immocare or hemchek or hem(W)chek or magstream or HemSP or bayer(W)detect or hemochaser or hemodia or bm(W)test or bmtest or colon(W)albumin
s s17:s29
s s16 and s30

PASCAL: Dialog. 1973-2004/07. 30th July 2004.

The PASCAL search covered the date range 1973 to July 2004. The search was carried out on 30th July 2004 and identified 690 records.

s (colorect? or colo rect?)(3N)(cancer? or neoplasm? or oncology? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (colon or colonic)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (rectal? or rectum?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (sigmoid? or rectosigmoi?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)bowel?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (lower(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s s1:s8
s occult(W)blood
s occult(W)bleed?
s blood?(3N)(stool? or fece? or faece?)
s (hidden(3N)blood?)
s fecal(W)occult or faecal(W)occult
s s10:s14
s s9 or s15
s fecal(W)occult(W)blood(W)(test? or measure?)
s faecal(W)occult(W)blood(W)(test? or measure?)
s fecal(W)occult(W)blood(W)(screen? or exam?)
s faecal(W)occult(W)blood(W)(screen? or exam?)
s stool(W)occult(W)blood(W)(test? or measure? or screen? or exam?)
s FOBT or FOB
s (stool? or fece? or faece?)(3N)(card or cards)
s (disposable or flushable)(3N)(reagent? or pad or pads or test? or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(W)chek or hemawipe or hema(W)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical?(3N)(test? or screen? or diagn?)
s immunologic?(3N)(test? or screen? or diagn?)
s colocare or hemeselect or immudia or flexsure or ez(W)detect? or immocare or hemchek or hem(W)chek or magstream or HemSP or bayer(W)detect or hemochaser or hemodia or bm(W)test or bmtest or colon(W)albumin
s s17:s29
s s16 and s30

Science Citation Index (SCI): ISI Web of Science. 1945/54-2004/July. 30th July 2004.

The SCI search covered the date range 1945/54 to July 2004. The search was carried out on 30th July 2004 and identified 1287 records.

TS=(colorectal cancer* or colorectal neoplasm* or colorectal tumo*r* or colorectal adenocarcinoma or colorectal carcinoma)
TS=(rectal cancer* or rectal neoplasm* or rectal tumo*r* or rectal adenocarcinoma or rectal carcinoma)
TS=(colon* cancer* or colon* neoplasm* or colon* tumo*r* or colon* adenocarcinoma or colon* carcinoma)
#1 or #2 or #3
TS=(occult blood or occult bleed*)
TS=(blood* same (stool* or fece* or faece*))
TS=(hidden same blood*)
TS=(fecal occult or faecal occult)
#5 or #6 or #7 or #8
#4 or #9
TS=(fecal occult blood test* or faecal occult blood test* or fecal occult blood measure* or faecal occult blood measure* or fecal occult blood screen* or faecal occult blood screen* or fecal occult blood exam* or faecal occult blood exam* or FOBT or FOB)
TS=(stool occult blood test* or stool occult blood measure* or stool occult blood screen* or stool occult blood exam*)
TS=((stool* or fece* or faece*) same (card or cards))
TS=((disposable or flushable) same (reagent* or pad or pads or test* or kit or kits))
TS=(guaiac or guiac)
TS=(haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema screen or hemachek or hema chek or hemawipe or hema wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin)
TS=(immunochemical* same (test* or screen* or diagn*))
TS=(immunologic* same (test* or screen* or diagn*))
TS=(colocare or hemeselect or immudia or flexsure or ez detect* or immocare or !nform or !nsure or hemchek or hem chek or magstream or HemSP or bayer detect or hemochaser or hemodia or bm-test or bmtest or colon albumin)
#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#10 and #20

Dissertation Abstracts: Dialog. 1861-2004/July. 30th July 2004.

The Dissertation Abstracts search covered the date range 1861 to July 2004. The search was carried out on 30th July 2004 and identified 25 records.

s (colorect? or colo rect?)(3N)(cancer? or neoplasm? or oncology? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (colon or colonic)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (rectal? or rectum?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (sigmoid? or rectosigmoi?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)s (cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum)(3N)(cancer? or neoplas?
or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)bowel?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)s (lower(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)

s s1:s8
s occult(W)blood
s occult(W)bleed?
s blood?(3N)(stool? or fece? or faece?)
s (hidden(3N)blood?)
s fecal(W)occult or faecal(W)occult
s s10:s14
s s9 or s15
s fecal(W)occult(W)blood(W)(test? or measure?)
s faecal(W)occult(W)blood(W)(test? or measure?)
s fecal(W)occult(W)blood(W)(screen? or exam?)
s faecal(W)occult(W)blood(W)(screen? or exam?)
s stool(W)occult(W)blood(W)(test? or measure? or screen? or exam?)
s FOBT or FOB
s (stool? or fece? or faece?)(3N)(card or cards)
s (disposable or flushable)(3N)(reagent? or pad or pads or test? or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(W)chek or hemawipe or hema(W)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical?(3N)(test? or screen? or diagn?)
s immunologic?(3N)(test? or screen? or diagn?)
s colocare or hemeselect or immudia or flexsure or ez(W)detect? or immocare or hemchek or hem(W)chek or magstream or HemSP or bayer(W)detect or hemochaser or hemodia or bm(W)test or bmtest or colon(W)albumin
s s17:s29
s s16 and s30

Inside Conferences: Dialog. 1993-2004/July. 30th July 2004.

The Inside Conferences search covered the date range 1993 to July 2004. The search was carried out on 30th July 2004 and identified 39 records.

s (colorect? or colo rect?)(3N)(cancer? or neoplasm? or oncology? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (colon or colonic)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (rectal? or rectum?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (sigmoid? or rectosigmoi?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (cecum or cecal or caecum or caecal or il?eoc?ecal or il?eoc?ecum)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)bowel?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (large(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s (lower(W)intestin?)(3N)(cancer? or neoplas? or oncolog? or malignan? or tumor? or tumour? or carcinoma? or adenocarcinoma?)
s s1:s8
s occult(W)blood
s occult(W)bleed?
s blood?(3N)(stool? or fece? or faece?)
s (hidden(3N)blood?)
s fecal(W)occult or faecal(W)occult
s s10:s14
s s9 or s15s fecal(W)occult(W)blood(W)(test? or measure?)
s faecal(W)occult(W)blood(W)(test? or measure?)
s fecal(W)occult(W)blood(W)(screen? or exam?)

s faecal(W)occult(W)blood(W)(screen? or exam?)
s stool(W)occult(W)blood(W)(test? or measure? or screen? or exam?)
s FOBT or FOB
s (stool? or fece? or faece?)(3N)(card or cards)
s (disposable or flushable)(3N)(reagent? or pad or pads or test? or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(W)chek or hemawipe or hema(W)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical?(3N)(test? or screen? or diagn?)
s immunologic?(3N)(test? or screen? or diagn?)
s colocare or hemeselect or immudia or flexsure or ez(W)detect? or immocare or hemchek or hem(W)chek or magstream or HemSP or bayer(W)detect or hemochaser or hemodia or bm(W)test or bmtest or colon(W)albumin
s s17:s29
s s16 and s30

Systems for Information in Grey Literature (SIGLE): WebSpirs. 1980-2004/06. 30th July 2004.

The SIGLE search covered the date range 1980 to June 2004. The search was carried out on 30th July 2004 and identified 1 record.

#1. (colorect* or colo rect*) near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#2. (colon or colonic) near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#3. (rectal* or rectum*) near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#4. (sigmoid or rectosigmoi*) near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#5. (c?ecum or c?ecal or il?eoc?ecal or il?eoc?ecum) near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#6. large bowel* near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#7. large intestin* near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#8. lower intestin* near3 (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#9. hepatic flexur* near (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#10. splenic flexur* near (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma*)
#11. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12. occult blood
#13. occult bleed*
#14. blood* near3 (stool* or fece* or faece*)
#15. hidden near3 blood*
#16. fecal occult or faecal occult
#17. #12 or #13 or #14 or #15 or #16
#18. #11 or #17
#19. fecal occult blood near (test* or measure*)
#20. faecal occult blood near (test* or measure*)
#21. fecal occult blood near (screen* or exam*)
#22. faecal occult blood near (screen* or exam*)
#23. FOBT or FOB
#24. stool occult blood near (test* or screen* or measure* or exam*)
#25. (stool* or fece* or faece*) near3 (card or cards)
#26. (disposable or flushable) near3 (reagent* or pad or pads or test* or kit or kits)
#27. guaiac or guiac

#28. haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema screen or hemachek or hema chek or hemawipe or hema wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
#29. immunochemical* near3 (test* or screen* or diagn*)
#30. immunologic* near3 (test* or screen* or diagn*)
#31. colocare or hemeselect or immudia or flexsure or ez detect* or immocare or hemchek or hem chek or magstream or HemSP or bayer detect or hemochaser or hemodia or bm test or bmtest or colon albumin
#32. #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
#33. #18 and #32

Latin American and Caribbean Literature on the Health Sciences (LILACS): BVS Virtual Health Library. 1982-2004/July. 30th July 2004.

The LILACS search covered the date range 1982 to July 2004. The search was carried out on 30th July 2004 and identified 3 records.

colorectal cancer$ or colorectal neoplasm$ or colorectal tumo$r$ or colorectal adenocarcinoma or colorectal carcinoma or rectal cancer$ or rectal neoplasm$ or rectal tumo$r$ or rectal adenocarcinoma or rectal carcinoma [words]

OR

occult blood or occult bleed$ or fecal occult or faecal occult or hidden blood$[words]

AND

f$ecal occult blood test$ or f$ecal occult blood screen$ or FOBT or FOB or disposable or flushable or guaiac or guiac or immunochemical$ test$ or immunochemical$ screen$ or immunochemical$ diagn$ or immunologic$ test$ or immunologic$ screen$ or immunologic$ diagn$[words]

NHS Economic Evaluation Database (NHS EED): Internal CRD database. 1995-2004/07. 30th July 2004.

The NHS EED search covered the date range 1995 to July 2004. The search was carried out on 30th July 2004 and identified 90 records.

S (colorect$ or colo rect$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (colon or colonic)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (rectal$ or rectum$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (sigmoid or rectosigmoi$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (c$ecum or c$ecal or ileocecal or ileocecum)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large bowel$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (lower intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (hepatic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (splenic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or

carcinoma$ or adenocarcinoma$)
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10
s occult(w)blood or occult(w)bleed$
s blood$(w3)(stool$ or fece$ or faece$)
s hidden(w3)blood$
s fecal(w)occult or faecal(w)occult
s s12 or s13 or s14 or s15
s s11 or s16
s fecal(w)occult(w)blood(w)(test$ or measure$) or faecal(w)occult(w)blood(w)(test$ or measure$)
s fecal(w)occult(w)blood(w)(screen$ or exam$) or faecal(w)occult(w)blood(w)(screen$ or exam$)
s stool(w)occult(w)blood(w)(test$ or measure$ or screen$ or exam$)
s FOBT or FOB
s (stool$ or fece$ or faece$)(w3)(card or cards)
s (disposable or flushable)(w3)(reagent$ or pad or pads or test$ or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(w)chek or hemawipe or hema(w)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical$(w3)(test$ or screen$ or diagn$)
s immunologic$(w3)(test$ or screen$ or diagn$)
s colocare or hemeselect or immudia or flexsure or ez(w)detect$ or immocare or hemchek or hem(w)chek or magstream or HemSP or bayer(w)detect or hemochaser or hemodia or bm(w)test or bmtest or colon(w)
albumin
s s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28
s s17 and s29

Health Economic Evaluation Database (HEED): OHE-IFPMA Database Ltd. 1988-2004/07. 30th July 2004.

The HEED search covered the date range 1988 to July 2004. The search was carried out on 30th July 2004 and identified 96 records.

AX=(colorectal cancer) or (colorectal cancers) or (colorectal neoplasm) or (colorectal neoplasms) or (colorectal tumor) or (colorectal tumors) or (colorectal tumour) or (colorectal tumours) or (colorectal carcinoma) or (colorectal carcinomas) or (colorectal adenocarcinoma)
AX=(colon cancer) or (colon cancers) or (colon neoplasm) or (colon neoplasms) or (colon tumor) or (colon tumors) or (colon tumour) or (colon tumours) or (colon carcinoma) or (colon carcinomas) or (colon adenocarcinoma)
AX=(rectal cancer) or (rectal cancers) or (rectal neoplasm) or (rectal neoplasms) or (rectal tumor) or (rectal tumors) or (rectal tumour) or (rectal tumours) or (rectal carcinoma) or (rectal carcinomas) or (rectal adenocarcinoma)
AX=(rectum cancer) or (rectum cancers) or (rectum neoplasm) or (rectum neoplasms) or (rectum tumor) or (rectum tumors) or (rectum tumour) or (rectum tumours) or (rectum carcinoma) or (rectum carcinomas) or (rectum adenocarcinoma)
CS=1 or 2 or 3 or 4
AX=(occult blood) or (occult bleed)
AX=blood* and stool*
AX=blood* and fece*
AX=blood* and faece*
AX=(fecal occult) or (faecal occult)
CS=6 or 7 or 8 or 9 or 10
CS=5 or 11
AX=(fecal occult blood test) or (fecal occult blood tests) or (faecal occult blood test) or (faecal occult blood tests)
AX=FOBT or FOB
AX=guaiac or guiac
AX=haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or (hema screen) or hemachek or (hema chek) or hemawipe or (hema wipe) or

monohaem or hemofec or hemofecia or fecatest or fecatwin
AX=immunochemical* and test*
AX=immunochemical* and screen*
AX=immunochemical* and diagn*
AX=immunologic* and test*
AX=immunologic* and screen*
AX=immunologic* and diagno*
AX= colocare or hemeselect or immudia or flexsure or (ez detect) or immocare or hemchek or (hem chek) or magstream or HemSP or (bayer detect) or hemochaser or hemodia or (bm test) or bmtest or (colon albumin)
CS=13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
CS=12 and 24

Database of Abstracts of Reviews of Effects (DARE): Internal CRD database. 1994-2004/08. 13th September 2004.

The DARE search covered the date range 1994 to August 2004. The search was carried out on 13th September 2004 and identified 31 records.

S (colorect$ or colo rect$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (colon or colonic)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (rectal$ or rectum$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (sigmoid or rectosigmoi$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (c$ecum or c$ecal or ileocecal or ileocecum)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large bowel$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (lower intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (hepatic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (splenic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10
s occult(w)blood or occult(w)bleed$
s blood$(w3)(stool$ or fece$ or faece$)
s hidden(w3)blood$
s fecal(w)occult or faecal(w)occult
s s12 or s13 or s14 or s15
s s11 or s16
s fecal(w)occult(w)blood(w)(test$ or measure$) or faecal(w)occult(w)blood(w)(test$ or measure$)
s fecal(w)occult(w)blood(w)(screen$ or exam$) or faecal(w)occult(w)blood(w)(screen$ or exam$)
s stool(w)occult(w)blood(w)(test$ or measure$ or screen$ or exam$)
s FOBT or FOB
s (stool$ or fece$ or faece$)(w3)(card or cards)
s (disposable or flushable)(w3)(reagent$ or pad or pads or test$ or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(w)chek or hemawipe or hema(w)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical$(w3)(test$ or screen$ or diagn$)
s immunologic$(w3)(test$ or screen$ or diagn$)
s colocare or hemeselect or immudia or flexsure or ez(w)detect$ or immocare or hemchek or hem(w)chek or magstream or HemSP or bayer(w)detect or hemochaser or hemodia or

bm(w)test or bmtest or colon(w)albumin
s s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28
s s17 and s29

Health Technology Assessment Database (HTA): Internal CRD database. 1994-2004/08. 13th September 2004.

The HTA search covered the date range 1994 to August 2004. The search was carried out on 13th September 2004 and identified 11 records.

S (colorect$ or colo rect$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (colon or colonic)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
S (rectal$ or rectum$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (sigmoid or rectosigmoi$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (c$ecum or c$ecal or ileocecal or ileocecum)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large bowel$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (large intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (lower intestin$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (hepatic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s (splenic flexur$)(3w)(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo$r$ or carcinoma$ or adenocarcinoma$)
s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10
s occult(w)blood or occult(w)bleed$
s blood$(w3)(stool$ or fece$ or faece$)
s hidden(w3)blood$
s fecal(w)occult or faecal(w)occult
s s12 or s13 or s14 or s15
s s11 or s16
s fecal(w)occult(w)blood(w)(test$ or measure$) or faecal(w)occult(w)blood(w)(test$ or measure$)
s fecal(w)occult(w)blood(w)(screen$ or exam$) or faecal(w)occult(w)blood(w)(screen$ or exam$)
s stool(w)occult(w)blood(w)(test$ or measure$ or screen$ or exam$)
s FOBT or FOB
s (stool$ or fece$ or faece$)(w3)(card or cards)
s (disposable or flushable)(w3)(reagent$ or pad or pads or test$ or kit or kits)
s guaiac or guiac
s haemoccult or haemoccult or haemoccultsensa or hemocare or seracult or coloscreen or hemascreen or hema(W)screen or hemachek or hema(w)chek or hemawipe or hema(w)wipe or monohaem or hemofec or hemofecia or fecatest or fecatwin
s immunochemical$(w3)(test$ or screen$ or diagn$)
s immunologic$(w3)(test$ or screen$ or diagn$)
s colocare or hemeselect or immudia or flexsure or ez(w)detect$ or immocare or hemchek or hem(w)chek or magstream or HemSP or bayer(w)detect or hemochaser or hemodia or bm(w)test or bmtest or colon(w)albumin
s s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26 or s27 or s28
s s17 and s29

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL). Cochrane Library, Update Software. Issue 3:2004. 13th September 2004.

The CDSR and CENTRAL were searched on the Cochrane Library on the 13th September 2004. 1 completed review was retrieved from the CDSR. 164 records were found on CENTRAL.

#1 COLORECTAL NEOPLASMS explode all trees (MeSH)
#2 CECAL NEOPLASMS explode all trees (MeSH)
#3 ((colorect* near cancer*) or (colorect* near neoplasm*) or (colorect* near malignan*) or (colorect* near oncolog*) or (colorect* near tumor*) or (colorect* near tumour*) or (colorect* near carcinoma*) or (colorect* near adenocarcinoma*))
#4 ((colon* near cancer*) or (colon* near neoplasm*) or (colon* near malignan*) or (colon* near oncolog*) or (colon* near tumor*) or (colon* near tumour*) or (colon* near carcinoma*) or (colon* near adenocarcinoma*))
#5 ((rectal* near cancer*) or (rectal* near neoplasm*) or (rectal* near malignan*) or (rectal* near oncolog*) or (rectal* near tumor*) or (rectal* near tumour*) or (rectal* near carcinoma*) or (rectal* near adenocarcinoma*))
#6 ((rectum* near cancer*) or (rectum* near neoplasm*) or (rectum* near malignan*) or (rectum* near oncolog*) or (rectum* near tumor*) or (rectum* near tumour*) or (rectum* near carcinoma*) or (rectum* near adenocarcinoma*))
#7 ((sigmoid* near cancer*) or (sigmoid* near neoplasm*) or (sigmoid* near malignan*) or (sigmoid* near oncolog*) or (sigmoid* near tumor*) or (sigmoid* near tumour*) or (sigmoid* near carcinoma*) or (sigmoid* near adenocarcinoma*))
#8 ((cecum* near cancer*) or (cecum* near neoplasm*) or (cecum* near malignan*) or (cecum* near oncolog*) or (cecum* near tumor*) or (cecum* near tumour*) or (cecum* near carcinoma*) or (cecum* near adenocarcinoma*))
#9 ((cecal* near cancer*) or (cecal* near neoplasm*) or (cecal* near malignan*) or (cecal* near oncolog*) or (cecal* near tumor*) or (cecal* near tumour*) or (cecal* near carcinoma*) or (cecal* near adenocarcinoma*))
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 OCCULT BLOOD single term (MeSH)
#12 (faecal next occult)
#13 (fecal next occult)
#14 FOBT or FOB
#15 guaiac or guiac
#16 ((immunochemical* near test*) or (immunochemical* near screen*) or (immunochemical* near diagn*))
#17 ((immunologic* near test*) or (immunologic* near screen*) or (immunologic* near diagn*))
#18 (#11 or #12 or #13 or #14 or #15 or #16 or #17)
#19 (#10 and #18)

National Research Register (NRR): Update Software. Issue 3:2004. 13th September 2004.

The NRR search was undertaken on issue 3 2004. The search was carried out on 13th September 2004 and identified 17 records.

#1 COLORECTAL NEOPLASMS explode all trees (MeSH)
#2 CECAL NEOPLASMS explode all trees (MeSH)
#3 ((colorect* near cancer*) or (colorect* near neoplasm*) or (colorect* near malignan*) or (colorect* near oncolog*) or (colorect* near tumor*) or (colorect* near tumour*) or (colorect* near carcinoma*) or (colorect* near adenocarcinoma*))
#4 ((colon* near cancer*) or (colon* near neoplasm*) or (colon* near malignan*) or (colon* near oncolog*) or (colon* near tumor*) or (colon* near tumour*) or (colon* near carcinoma*) or (colon* near adenocarcinoma*))
#5 ((rectal* near cancer*) or (rectal* near neoplasm*) or (rectal* near malignan*) or (rectal* near oncolog*) or (rectal* near tumor*) or (rectal* near tumour*) or (rectal* near carcinoma*) or (rectal* near adenocarcinoma*))

#6 ((rectum* near cancer*) or (rectum* near neoplasm*) or (rectum* near malignan*) or (rectum* near oncolog*) or (rectum* near tumor*) or (rectum* near tumour*) or (rectum* near carcinoma*) or (rectum* near adenocarcinoma*))
#7 ((sigmoid* near cancer*) or (sigmoid* near neoplasm*) or (sigmoid* near malignan*) or (sigmoid* near oncolog*) or (sigmoid* near tumor*) or (sigmoid* near tumour*) or (sigmoid* near carcinoma*) or (sigmoid* near adenocarcinoma*))
#8 ((cecum* near cancer*) or (cecum* near neoplasm*) or (cecum* near malignan*) or (cecum* near oncolog*) or (cecum* near tumor*) or (cecum* near tumour*) or (cecum* near carcinoma*) or (cecum* near adenocarcinoma*))
#9 ((cecal* near cancer*) or (cecal* near neoplasm*) or (cecal* near malignan*) or (cecal* near oncolog*) or (cecal* near tumor*) or (cecal* near tumour*) or (cecal* near carcinoma*) or (cecal* near adenocarcinoma*))
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
#11 OCCULT BLOOD single term (MeSH)
#12 (faecal next occult)
#13 (fecal next occult)
#14 FOBT or FOB
#15 guaiac or guiac
#16 ((immunochemical* near test*) or (immunochemical* near screen*) or (immunochemical* near diagn*))
#17 ((immunologic* near test*) or (immunologic* near screen*) or (immunologic* near diagn*))
#18 (#11 or #12 or #13 or #14 or #15 or #16 or #17)
#19 (#10 and #18)

National Technical Information Service (NTIS): U.S. Department of Commerce web site. 1990-2004. 13th September 2004.

The NTIS search covered the date range 1990 to August 2004. The search was carried out on 13th September 2004 and identified 1 record. Each line was searched separately.

'feacal occult'
'fecal occult'
FOBT
FOB

GrayLIT Network: U.S. Office of Scientific and Technical Information web site. August 2004. 13th September 2004.

The GrayLit search was carried out on 13th September 2004 and identified 0 records. Each line was searched separately.

'Fecal occult'
'Faecal occult'
fobt
fob
'occult blood'

Internet searches

Additional searches were undertaken on the Internet. The searches were very simple and only the first 100 hits from the Google searches were browsed. Most of the results referred to studies already retrieved in the database searches, patient information sites, and FOBT manufacturer sites. Any results that had not been previously identified were added to the EndNote library of results from the database searches.

OMNI (Organising Medical Networked Information). Health Information Resources Gateway. 13th September 2004.
http://omni.ac.uk

Each line was searched separately. Truncation was automatic.

Fecal occult
Faecal occult
fobt
fob
occult blood

Copernic. Meta-Search Engine. 13th September 2004.
http://www.copernic.com

Each line was searched separately.

Fecal occult blood test
Faecal occult blood test

Google. Search Engine. 13th September 2004.
www.google.co.uk

Each line searched separately. The first 100 hits were checked for anything that had not been already been identified.

Fecal occult blood test
Faecal occult blood test

Update searches

Update searches were undertaken on the 25th November using the same search strategies used in the original searches.

MEDLINE: Ovid gateway. 2004/Jul week 4 - 2004/Nov week 3. 25th November 2004.

The update MEDLINE search covered the date range July to November 2004. The search was carried out on 25th November 2004 and identified 44 records.

EMBASE: Ovid gateway. 2004/week 30 - 2004/week 47. 25th November 2004.

The update EMBASE search covered the date range July to November 2004. The search was carried out on 25th November 2004 and identified 45 records.

BIOSIS: Dialog. 2004. 25th November 2004.

The update BIOSIS search covered the year 2004. The search was carried out on 25th November 2004 and identified 59 records.

PASCAL: Dialog. 2004. 25th November 2004.

The update PASCAL search covered the year 2004. The search was carried out on 25th November 2004 and identified 31 records.
Science Citation Index (SCI): ISI Web of Science. 2004. 25th November 2004.

The update SCI search covered the year 2004. The search was carried out on 25th November 2004 and identified 100 records.

Dissertation Abstracts: Dialog. 2004. 25th November 2004.

The update Dissertation Abstracts search covered the year 2004. The search was carried out on 25th November 2004 and identified 0 records.

Inside Conferences: Dialog. 2004. 25th November 2004.

The update Inside Conferences search covered the year 2004. The search was carried out on 25th November 2004 and identified 0 records.

Systems for Information in Grey Literature (SIGLE): WebSpirs. 2004/06.

An update search of SIGLE could not be undertaken, as the database had not been updated since the original searches.

Latin American and Caribbean Literature on the Health Sciences (LILACS): BVS Virtual Health Library. 2004/July - 2004/November. 25th November 2004.

The update LILACS search covered the date range July to November 2004. The search was carried out on 25th November 2004 and identified 0 records.

NHS Economic Evaluation Database (NHS EED): Internal CRD database. 2004/07 – 2004/10. 25th November 2004.

The update NHS EED search covered the date range July to October 2004. The search was carried out on 25th November 2004 and identified 9 records.

Health Economic Evaluation Database (HEED): OHE-IFPMA Database Ltd. 2004/07 – 2004/11. 25th November 2004.

The update HEED search covered the date range July to November 2004. The search was carried out on 25th November 2004 and identified 0 records.

Database of Abstracts of Reviews of Effects (DARE): Internal CRD database. 2004/07 – 2004/10. 25th November 2004.

The update DARE search covered the date range July to October 2004. The search was carried out on 25th November 2004 and identified 1 record.

Health Technology Assessment Database (HTA): Internal CRD database. 2004/07 – 2004/10. 25th November 2004.

The update HTA search covered the date range July to October 2004. The search was carried out on 25th November 2004 and identified 4 records.

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL). Cochrane Library, Update Software. Issue 4:2004. 25th November 2004.

The CDSR and CENTRAL were searched on the Cochrane Library on the 25th November 2004. The search was restricted to references added since the previous issue. 1 protocol was retrieved from the CDSR. 2 records were found on CENTRAL.

National Research Register (NRR): Update Software. Issue 4:2004. 25th November 2004.

The update NRR search was undertaken on issue 4 2004 and restricted to references added since the previous issue. The search was carried out on 25h November 2004 and identified 2 records.

National Technical Information Service (NTIS): U.S. Department of Commerce web site. 2004. 25th November 2004.

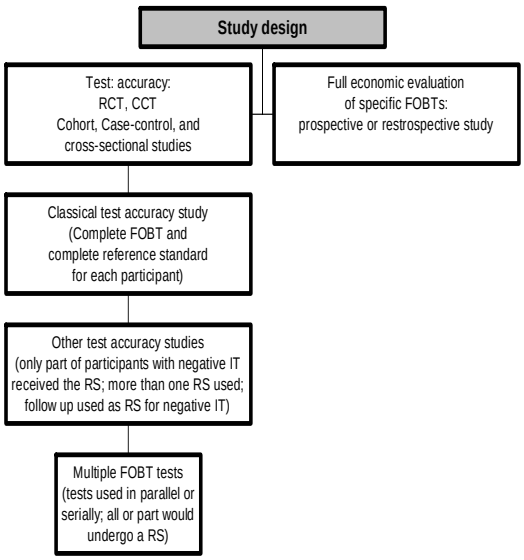
The update NTIS search covered the year 2004. The search was carried out on 25th November 2004 and identified 0 records.

GrayLIT Network: U.S. Office of Scientific and Technical Information web site. November 2004. 25th November 2004.

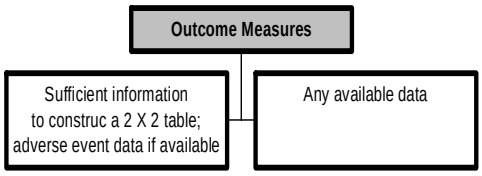
The update GrayLit search was carried out on 25th November 2004 and identified 0 records.

APPENDIX D: CHECKLIST WITH EXPLICIT INCLUSION AND EXCLUSION CRITERIA

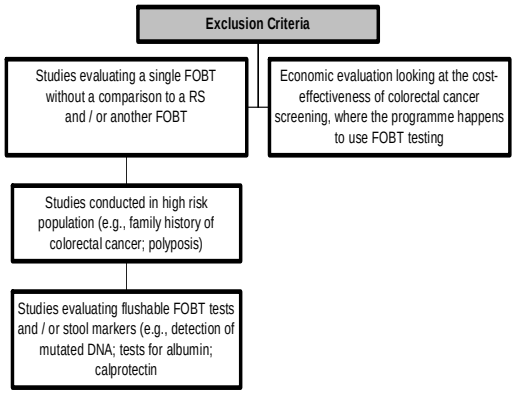
1. When checking the references include studies if they present the following design:



2. AND the following outcome measures



3. Exclude all studies listed on this box



4. If while checking the references you say YES for 1 and 2

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APPENDIX E: PRE-DEFINED CHECKLIST FORM USED TO CONSTRUCT THE MICROSOFT ACCESS DATABASE

Study details and aims	Study population	Details of diagnostic test(s) and reference (gold) standard	Results	Conclusions and comments
Author, year and endnote ref no. **Country:** **Setting:** **Study design:** **Aims:** **N° participants:** **Follow-up:**	**Description of included participants:** Age Gender Ethnicity Potential risk factors **Predefined inclusion/exclusion criteria:** **Diet restrictions and any measure of adherence to them:** **Additional population data:** Method patient selection Disease prevalence **Number of participants recruited/included in analyses (in each group):** **Number of participants that received (in each group):** **Index test** **Reference standard**	**Type of diagnostic test(s):** *Guaiac / Immunochemistry* *Type of IC test/methodology:* Test performance: **Sequence of tests:** **Name of test(s):** **Test technique:** **Method of development and location:** Number of stool samples and sampling modalities: **Frequency of test:** **Process involved:** **Reference standard(s) used:** Complications Staff experience Preparation of colon for procedure Completeness	**TP:** **FP:** **TN:** **FN:** **For the detection of cancers:** Sensitivity = % (95% CI:) Specificity = % (95% CI:) Accuracy = % (95% CI:) Positive likelihood ratio = % (95% CI:) Negative likelihood ratio = % (95% CI:) Positive predictive vale = % (95% CI:) Negative predictive vale = % (95% CI:) Diagnostic odds ratio = % (95% CI:) **For the detection of polyps ≥1cm:** Sensitivity = % (95% CI:) Specificity = % (95% CI:) Accuracy = % (95% CI:) Positive likelihood ratio = % (95% CI:) Negative likelihood ratio = % (95% CI:) Positive predictive vale = % (95% CI:) Negative predictive vale = % (95% CI:) Diagnostic odds ratio = % (95% CI:) **Other subgroup analyses:** **Patient outcomes for RCTs:** Survival Stage of disease **Adverse events:**	**Author's conclusions:** **Comments:**

APPENDIX F: QUADAS AND DETAILS OF CRITERIA FOR SCORING STUDIES

1.	**Was the spectrum of patients representative of the patients who will receive the test in practice?**
Yes	Unselected screening population or consecutive cohort of average risk people
No	All other patient spectra
Unclear	If insufficient details were provided to make a judgement as to whether the patient spectrum would be scored as “yes”.

2.	**Were selection criteria clearly described?**
Yes	Enough details are provided of how patients were selected so that the selection process could be replicated.
No	Insufficient details are presented.
Unclear	Not applicable.

3.	**Is the reference standard likely to correctly classify the target condition?**
Yes	Colonoscopy +/- histopathology
No	All other reference standards.
Unclear	If details of the reference standard are not reported.

Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
As the disease progression of CRC is slow, it was considered most appropriate to restrict the maximum length of follow-up acceptable in studies to 10 years, hence this criteria was not scored during the QUADAS assesment.

4.	**Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?**
Yes	If the whole sample or a random selection of the sample received a reference standard.
No	If only a selected sample received the reference standard.

Unclear	If it is not clear whether all the patients the reference standard.

5.	**Did patients receive the same reference standard regardless of the index test result?**
Yes	If all patient, +ve and –ve FOBT, received the same reference standard.
No	If some patients received a different reference standard.
Unclear	If it is not clear whether all patients received the same reference standard.

Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
This was considered not to be applicable to a review of FOBTs.

6a.	**Was the execution of the index test described in sufficient detail to permit replication of the test?**
6b.	**Was the execution of the reference standard described in sufficient detail to permit its replication?**
Yes	If sufficient details of test execution are reported so that all the required details can be completed on the data extraction forms
No	If sufficient details are not reported
Unclear	Not applicable

7a.	**Were the index test results interpreted without knowledge of the results of the reference standard?**
7b.	**Were the reference standard results interpreted without knowledge of the results of the index test?**
Yes	If the index test was interpreted without knowledge of the results of the reference standard and vice versa.
No	If the person interpreting the index test was aware of the results of the reference standard or vice versa.
Unclear	If no information is provided regarding whether tests were interpreted blindly.

8.	**Were the same clinical data available when index test results were interpreted as would be available when the index test is used in practice?**
Yes	The results of all other tests should be available to the person interpreting the results of the index test
No	If not as above.
Unclear	If details on the availability of clinical data are not reported.

9.	**Were uninterpretable/ intermediate test results reported?**
Yes	If details are provided on uninterpretable / intermediate test results.
No	If there appear to be some uninterpretable / intermediate but the results of these are not reported.
Unclear	If it is not clear whether there were any uninterpretable/ intermediate test results.

10.	**Were withdrawals from the study explained?**
Yes	If all patients recruited into the study were accounted for.
No	If there appear to be patients who were recruited into the study who are not accounted for.
Unclear	If it is not clear whether any withdrawals occurred.

APPENDIX G: DETAILS OF STUDIES INCLUDED ON THIS REVIEW

Table 21: Guaiac FOBTs included studies

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Allison (1990)[64]	Diagnostic cohort (Screening population) n=15 188 Age=45-70+ Location=USA	Haemoccult II	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour diffusing 5mm in 1 minute	Colonoscopy or barium enema, and registry	Registry
Allison (1996)[8]	Diagnostic cohort (Screening population) n=8104 Age=50-70+ Location=USA	Haemoccult II Haemoccult SENSA	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour diffusing 5mm in 1 minute	Colonoscopy and follow-up	Follow-up and registry
Allison (2002)[5]	Diagnostic cohort (screening population) N=5932 Age=50-70+ Location=USA	Haemoccult SENSA	Definition of a posititve result: Not reported	Colonoscopy	Flexible colonoscopy
Bang (1986)[65]	Diagnostic cohort n=1473 Age=20+ Location=USA	Haemoccult II	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour within 30 seconds	Colonoscopy and/or barium enema	Sigmoidoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Bennett (1996)[93]	Diagnostic cohort n=2909 Age=50-74 Location=Denmark	Haemoccult	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Flexible sigmoidoscopy	Flexible sigmoidoscopy
Bhattacharya (1997)[81]	Diagnostic case-control n=72 Cases n=168 Controls Location=USA	Haemoccult	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Colonoscopy	Colonoscopy
Brevinge (1997)[107]	RCT n=825 Age=55-56 Location=Sweden	Haemoccult II	Rehydration: Yes Dietary restrictions: On repeated testing after a positive first test Definition of a positive results: Not reported	Flexible sigmoidoscopy and Barium enema	Flexible sigmoidoscopy
Castiglione (1991)[94]	Diagnostic cohort (Screening population**)** n=14 992 Age=40-70 Location=Italy	Haemoccult	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Not reported	Sigmoidoscopy and barium enema	Rescreening and registry
Collins (2005)[97]	Diagnostic cohort (Screening population) n=3121 Age=50-75 Location=USA	Haemoccult II (home) Haemoccult II (DRE*)	Rehydration: Yes (3-days home test); No (DRE test) Dietary restrictions: Yes Definition of a positive results: Not reported	Colonoscopy	Colonoscopy

* DRE = Digital Rectal Examination

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Foley (1992)[67]	Diagnostic cohort (Screening population) n=900 Age=44-85 Location=Ireland	Haemoccult	Rehydration: Yes Dietary restrictions: Yes Definition of a positive results: Any blue colour within 1 minute	Sigmoidoscopy - unspecified	Sigmoidoscopy - unspecified
Kikkawa (1987)[6]	Diagnostic case-control n=30 Cases n=30 Controls Location=Japan	Haemoccult II	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Unclear	Unclear
Klug (1983)[68]	Diagnostic cohort n=790 Age=45+ Location=Germany	KryptoHaem	Rehydration: Not reported Dietary restrictions: Yes Definition of a positive results: Any blue/green colour within 30 seconds	Barium enema and sigmoidoscopy - unspecified	Rigid sigmoidoscopy
Lampe (1982)[83]	Diagnostic case-control n=154 Cases n=257 Controls Location=Germany	KryptoHaem	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Unclear	Unclear
Launoy (1997)[69]	Diagnostic cohort (Screening population**)** n=71307 Age=45-74 Location=France	Haemoccult II	Rehydration: No Dietary restrictions: No Definition of a positive results: Not reported	Colonoscopy	Registry

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Lieberman (2001)[70]	Diagnostic cohort n=2885 Age=50-75 Location=USA	Haemoccult II	Rehydration: Yes Dietary restrictions: Not reported Definition of a positive results: Not reported	Colonoscopy	Sigmoidoscopy
Lindholm (1997)[109]	Adverse events only – No 2x2 data	Guaiac	N/A	N/A	N/A
Mandel (1989)[110]	RCT n=97 205 Age=50-80 Location=USA	Haemoccult II	Rehydration: No 1975-1977; Some 1977-1982; Yes 1982 onwards Dietary restrictions: Yes Definition of a positive results: Not reported	Colonoscopy (Barium enema in 5%)	Annual questionnaire
Mant (1990)[111]	Adverse events only – No 2x2 data	Guaiac	N/A	N/A	N/A
Matsuse (1989) [2]	Diagnostic case-control n n=44 Cases n=46 Controls Location=Japan	Unclear	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Colonoscopy and barium enema	Colonoscopy and barium enema
Michalek (1988)[100]	Diagnostic cohort (Screening population) n=11 497 Age=40+ Location=USA	Haemoccult II	Rehydration: Not reported Dietary restrictions: Yes Definition of a positive results: Not reported	Questionnaire, GP contact and registry	Registry
Miyoshi (1988) [1]	Diagnostic case-control n=44 Cases n=28 Controls Location=Japan	Unclear	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Unclear	Unclear

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Miyoshi (1992) [9]	Diagnostic case-control n=46 Cases n=33 Controls Location=Japan	Haemoccult II Shinogi B	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Colonoscopy and histology	Colonoscopy or barium enema
Murakami (1992)[72]	Diagnostic cohort (Screening population**)** n=3449 Age=39-70 Location=Japan	Shinogi B	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Not reported	Registry	Registry
Nakama (1994)[7]	Diagnostic case-control n=200 Cases n=100 Controls Location=Japan	Haemoccult II	Rehydration: Not reported Dietary restrictions: No Definition of a positive results: Not reported	Colonoscopy and barium enema	Upper and lower tract endoscopy
Niv (2002)[112]	Diagnostic cohort n=2538 Age=40-75 Location=Israel	Haemoccult II	Rehydration: No Dietary restrictions: Not reported Definition of a positive results: Not reported	Colonoscopy	Registry
Parikh (2001)[77]	Diagnostic cohort n=362 Age=45-84 Location=USA	Haemoccult	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour within 1 minute	Colonoscopy	Flexible sigmoidoscopy
Parker (2002)[104]	Adverse events only – No 2x2 data	Guaiac	N/A	N/A	N/A

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Rasmussen (1999)[113]	RCT n=2222 Age=50-74 Location=Denmark	Haemoccult II	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour	Colonoscopy and barium enema	Flexible sigmoidoscopy
Rennert (2001)[105]	Diagnostic cohort (Screening population) n=22 193 Age=50-74 Location=Israel	Haemoccult SENSA	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Not reported	Colonoscopy	Rescreening and Registry
Ribet (1980)[78]	Diagnostic cohort n=230 Age=Not reported Location=France	Haemoccult	Rehydration: Not reported Dietary restrictions: Yes Definition of a positive results: Not reported	Colonoscopy, rigid sigmoidoscopy and barium enema	Rigid sigmoidoscopy and barium enema
St John (1992)[79]	Diagnostic case-control n=210 Cases n=150 Controls Location=Australia	Haemoccult II	Rehydration: No Dietary restrictions: Yes Definition of a positive results: Any blue colour witin 1 minute	Colonoscopy	Colonoscopy
St John (1993)[10]	Diagnostic case-control n=188 Cases n=50 Controls Location=Australia	Haemoccult SENSA	Rehydration: Not reported Dietary restrictions: Yes Definition of a positive results: Any blue colour within 1 minute	Colonoscopy	Unclear

Study ID	Study details	Index Test	Test details	Reference Standard after a +veFOBT or in cases	Reference Standard after a -veFOBT or in controls
Sung (2003)[80]	Diagnostic cohort n=505 Age=50-79 Location=Hong Kong	Haemoccult II	Rehydration: No Dietary restrictions: No Definition of a positive results: Not reported	Colonoscopy	Colonoscopy
Takeshita (1982)[3]	Diagnostic case-control n=24 Cases n=20 Controls Location=Japan	Shionogi B	Rehydration: Not reported Dietary restrictions: Not reported Definition of a positive results: Not reported	Unclear	Unclear
Takeshita (1985)[4]	Diagnostic case-control n=60 Cases n=30 Controls Location=Japan	Shionogi B	Rehydration: Not reported Dietary restrictions: No Definition of a positive results: Not reported	Unclear	Unclear
Winawer (1980)[106]	Diagnostic cohort (Screening population) n=5549 Age=Mean 40 (No range reported) Location=USA	Haemoccult	Rehydration: Not reported Dietary restrictions: Yes Definition of a positive results: Not reported	Sigmoidoscopy – unspecified and barium enema	Sigmoidoscopy – unspecified

Table 22: Immunochemical FOBTs included studies

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Allison (1996)[8]	Diagnostic cohort (Screening population) n=8104 Age=50-70+ Location=USA	HemeSelect/ Immudia HemSp	Definition of a positive result: Agglutination at 1:8 dilution	Colonoscopy and follow up	Follow-up and registry
Allison (2002)[5]	Diagnostic cohort (screening population) N=5932 Age=50-70+ Location=USA	FlexSure	Definition of a posititve result: Not reported	Colonoscopy	Flexible colonoscopy
Chen (1997)[95]	Diagnostic cohort (Screening population) n=62 611 Age=30-60+ Location=China	RPHA	Definition of a positive result: Not reported	Flexible sigmoidoscopy	Follow-up
Chen (2002)[66]	Diagnostic cohort n=2187 Age=29-87 Location=Taiwan	Unclear	Definition of a positive result: Not reported	Colonoscopy	Colonoscopy
Cheng (2002)[96]	Diagnostic cohort (Screening population) n=7411 Age=20-80+ Location=Taiwan	OC Hemodia/OC Hemocatch	Definition of a positive result: Not reported	Colonoscopy	Colonoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Gondal (2003)[108]	RCT =6266 Age=50-64 Location=Norway	FlexSure	Definition of a positive result: Not reported	Colonoscopy	Flexible sigmoidoscopy
Itoh (1996)[98]	Diagnostic cohort (Screening population) n=27860 Age=40+ Location=Japan	OC Hemodia/OC Hemocatch	Definition of a positive result: Agglutination within 3 minutes	Colonoscopy	Health insurance claims
Kawai (1987) [82]	Diagnostic case-control n=126 Cases n=197 Controls Location=Japan	Monohaem	Definition of a positive result: Not reported	Colonoscopy and barium enema	Colonoscopy and barium enema
Kikkawa (1987)[6]	Diagnostic case-control n=30 Cases n=30 Controls Location=Japan	Latex cohesion method Feca-EIA	Definition of a positive result: Not reported	Unclear	Unclear
Kim (1998)[99]	Diagnostic cohort n=7251 Age=Not reported Location=Korea	OC Hemodia/OC Hemocatch	Definition of a positive result: Not reported	Flexible sigmoidoscopy	Flexible sigmoidoscopy
Liu (2003)[71]	Diagnostic cohort n=1387 Age=46 +/-12.1 years Location=Taiwan	OC Hemodia/OC Hemocatch	Definition of a positive result: Not reported	Colonoscopy	Colonoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Matsuse (1989) [2]	Diagnostic case-control n=44 Cases n=46 Controls Location=Japan	LA Hemochaser EIA Checkmate Hemo OC Hemodia/OC Hemocatch Imdia Hem Sp	Definition of a positive result: LA Hemochaser: visible cohesion after 3 minutes; Other FOBTs: Not reported	Colonoscopy and barium enema	Colonoscopy and barium enema
Miyoshi (1988) [1]	Diagnostic case-control n=44 Cases n=28 Controls Location=Japan	Feca EIA Monohaem Imdia Hem Sp Hemo EIA Stick EIA	Definition of a positive result: Not reported	Unclear	Unclear
Miyoshi (1992) [9]	Diagnostic case-control n=46 Cases n=33 Controls Location=Japan	Feca EIA	Definition of a positive result: Not reported	Colonoscopy and histology	Colonoscopy or barium enema
Morikawa (2004)[101]	Diagnostic cohort (Screening population**)** n=22 743 Age=Mean 48 (No range reported) Location=Japan	Unclear	Definition of a positive result: Not reported	Colonoscopy	Colonoscopy
Nakama (1994)[7]	Diagnostic case-control n=200 Cases n=100 Controls Location=Japan	Monohaem	Definition of a positive result: Development of a green colour	Colonoscopy and barium enema	Colonoscopy and barium enema

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Nakama (1996)[87]	Diagnostic case-control n=150 Cases n=300 Controls Location=Japan	OC Hemodia/OC Hemocatch	Definition of a positive result: Agglutination within 3 minutes	Colonoscopy	Upper and lower tract endoscopy
Nakama (1996)[102]	Diagnostic cohort (Screening population**)** n=3365 Age=40-80+ Location=Japan	MonoHaem	Definition of a positive result: Appearance of a green colour	Colonoscopy (Barium enema in 2%)	Follow-up and registry
Nakama (1997)[86]	Diagnostic case-control n=276 Cases n=130 Controls Location=Japan	OC Hemodia/OC Hemocatch	Definition of a positive result: Agglutination withing 3 minutes	Colonoscopy	Colonoscopy
Nakama (2000)[74]	Diagnostic cohort (Screening population**)** n=17664 Age=40-60 Location=Japan	Iatro Hemcheck	Definition of a positive result: No agglutination within 1.5 minutes	Colonoscopy	Colonoscopy
Nakama (2000)[75]	Diagnostic cohort (Screening population**)** n=1044 Age=Not reported Location=Japan	MonoHaem	Definition of a positive result: Appearance of a green colour	Colonoscopy	Colonoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Nakama (2000)[42]	Diagnostic case-control n=250 Cases n=250 Controls Location=Japan	Iatro Hemcheck Imdia Hem Sp LA Hemochaser MonoHaem OC Hemodia/OC Hemocatch	Definition of a positive result: Agglutination at 1:8 dilution	Colonoscopy	Upper and lower tract endoscopies
Nakama (2001)[73]	Diagnostic cohort (Screening population) n=9952 Age=Mean 54 (No range given) Location=Japan	Imdia Hem Sp	Definition of a positive result: Agglutination at 1:8 dilution	Colonoscopy	Colonoscopy
Nakama (2004)[85]	Diagnostic case-control n=82 Cases n=320 Controls Location=Japan	OC Hemodia/OC Hemocatch	Definition of a positive result: Agglutination within 3 minutes	Colonoscopy and pathology	Upper and lower tract endoscopy
Nakama(2000)[76]	Diagnostic cohort n=9625 Age=40-60+ Location=Japan	MonoHaem	Definition of a positive result: Appearance of a green colour	Colonoscopy	Colonoscopy
Okamoto (1997)[103]	Diagnostic cohort n=5648 Age=Mean 48 (Range not reported) Location=Japan	RPHA	Definition of a positive result: Not reported	Colonoscopy	Colonoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
St John (1993)[10]	Diagnostic case-control n=188 Cases n=50 Controls Location=Australia	HemeSelect/Immudia HemSp	Definition of a positive result: Agglutination at 1:8 dilution	Colonoscopy	Unclear
Tada (1986)[88]	Diagnostic case-control n=65 Cases n=137 Controls Location=Japan	Feca-EIA OC Hemodia/OC Hemocatch	Definition of a positive result: Feca-EIA: Not reported; OC Hemodia: Agglutination after 3 minutes	Colonoscopy and barium enema	Colonoscopy and barium enema
Tada (1988)[89]	Diagnostic case-control n=72 Cases n=121 Controls Location=Japan	Iatro Hemcheck OC Hemodia/OC Hemocatch	Definition of a positive result: Not reported	Unclear	Unclear
Takeshita (1982)[3]	Diagnostic case-control n=24 Cases n=20 Controls Location=Japan	Ouchterlony	Definition of a positive result: Not reported	Unclear	Unclear
Takeshita (1985)[4]	Diagnostic case-control n=60 Cases n=30 Controls Location=Japan	Ouchterlony	Definition of a positive result: Not reported	Unclear	Unclear
Zhang (2002)[90]	Diagnostic case-control n=114 Cases n=228 Controls Location=Japan	Iatro Hemcheck	Definition of a positive result: No agglutination within 1.5 minutes	Colonoscopy and biopsy	Upper and lower tract endoscopy

Study ID	Study details	Index Test	Test details	Reference Standard after a positive FOBT or in cases	Reference Standard after a negative FOBT or in controls
Zhou (1987)[91]	Diagnostic case-control n=19 Cases n=50 Controls Location=China	RPHA	Definition of a positive result: Not reported	Unclear	Unclear
Zhou (1993)[46]	Diagnostic cohort (Screening population) n=2660 Age=40+ Location=China	SPA test	Definition of a positive result: Agglutination within 3 minutes	Sigmoidoscopy - unspecified	Sigmoidoscopy - unspecified
Zhu (1988)[92]	Diagnostic case-control n=63 Cases n=39 Controls Location=China	HemeSelect/Immudia HemSp	Definition of a positive result: Agglutination with sensitised cells at 2^3	Unclear	Unclear

Table 23: Sequential FOBT included study

Study ID	Study details	Index Test	Test details	Reference Standard after a negative FOBT	Reference Standard after a positive FOBT
Li (1995)[84]	Diagnostic case-control n=147 Cases n= 475 Controls Location= China	Guaiac followed by immunochemical (both unspecified)	Definition of a positive result: Not reported	Colonoscopy and pathology	Unclear

Table 24: Included Economic Evaluations

Study ID	Index Test	Benefit	Perspective/ Location	Costs
Ballegooijen (2003)[116]	Haemoccult II Haemoccult Sensa Immunochemical (unspecified)	Life years saved (CRC and adenomas)	Third party payer Location=USA	Direct: Test; Follow-up; Surveillance; Treatment Indirect: None reported
Berchi (2004)[118]	Haemoccult Magstream/Hem SP	Life years saved (CRC and adenomas)	French Social Security Service Location=France	Direct: Test purchase, distribution, revelation; Colonoscopy; Treatment Indirect: None reported
Castiglione (1997)[117]	Haemoccult RPHA	Cost per CRC/adenoma detectd	Health Service Location=Italy	Direct: Staff; General expenses; Buildings; Recruitment into study; Assessment Indirect: None reported
Daniels (1995)[114]	Haemoccult Okokit II	Cost per CRC case detectd	Payer (RAF) Location=UK	Direct: FOBT; Personal costs of testing; Follow-up Indirect: None reported
Shimbo (1994)[119]	Guaiac Immunochemical (Both unspecified)	Life years saved (CRC and adenomas)	Payer Location=Japan	Direct: FOBT; Follow-up; Complications; Treatment Indirect: None reported
Walker (1992)[115]	Haemoccult Coloscreen HemeSelect Feca EIA	Cost per CRC case detectd	Health Service Location=UK	Direct: Unclear Indirect: None reported
Wong (2004)[120]	Guaiac Immunochemical (Both unspecified)	Life expectancy (CRC only)	Not reported Location=Singapore	Direct: Screening procedure; Complications; Treatment Indirect: None reported

APPENDIX H: DETAILS OF STUDIES EXCLUDED FROM THIS REVIEW

1021 of the 1089 articles ordered were received and screened, with the remaining 68 being unobtainable. Of these 1021, 260 were either letters, comments, discussion documents or reviews that would not have been considered relevant to the current review, and are therefore not included in the following tables. Sixty-nine studies were included in the review, and 692 potentially relevant studies did not meet the inclusion criteria for the review and were excluded. Diagnostic accuracy studies that were excluded are listed in Tables 25 and 26, and economic evaluations in table 27.

The diagnostic accuracy studies were excluded from the review for the following reasons:

1. Insufficient data to produce a 2x2 table
2. High risk population
3. High drop out rate on rescreening or follow-up
4. No reported reference standard
5. Cases had general gastrointestinal disease, not specifically colorectal cancer
6. Blood ingested or added to stool
7. Duplicate reports
8. Other reasons for exclusion (listed separately in table 26 with reasons stated)

Table 25: Diagnostic accuracy studies, RCTs, and screening studies that were excluded from the review, and the reasons for their exclusion

Adams (1974)[145] **6**	Hardcastle (1985)[146] **1**	Olynyk (2001)[147] **1**
Adamsen (1984)[148] **1**	Hardcastle (1986)[149] **3**	Ookata (1985)[150] **2**
Adlercreutz (1978)[151] **4**	Hardcastle (1989)[152] **3**	Ostrow (1973)[153] **6**
Adlercreutz (1980)[154] **2**	Hardcastle (1991)[155] **7**	Otto (1990)[156] **1**
Adlercreutz (1984)[157] **2**	Hardcastle (1994)[158] **1**	Otto (2004)[159] **1**
Agusti (2004)[160] **1**	Hardcastle (1996)[28] **3**	Panzer (1995)[161] **1**
Ahlquist (1990)[162] **2**	Hart (1994)[163] **1**	Parikh (2000)[164] **2**
Ahlquist (1993)[165] **2**	Hart (1997)[166] **1**	Parra-Blanco (2004)[167] **1**
Ahlquist (1993)[168] **2**	Hart (1998)[169] **1**	Pavlides (1977)[170] **2**
Aisawa (1980)[171] **1**	Hart (2003)[172] **1**	Pearson (2000)[31] **1**
Ajam (1990)[173] **1**	Hastings (1974)[174] **3**	Petrelli (1989)[175] **1**
Akagi (1993)[176] **1**	Hatfield (1983)[177] **1**	Petrelli (1994)[178] **1**
Ali (2003)[179] **1**	Heeb (1978)[180] **1**	Porschen (1993)[181] **1**
Allison (1992)[182] **1**	Heim (1986)[183] **1**	Prasler (1992)[184] **2**
Allison (1993)[185] **1**	Helfrich (1977)[186] **1**	Preisich (1987)[187] **1**
Allison (2002)[5] **7**	Herrinton (1995)[188] **2**	Protell (1979)[189] **2**
Angelici (1993)[190] **1**	Herzog (1979)[191] **2**	Pye (1987)[192] **1**

Armbrecht (1994)[193] **2**	Herzog (1983)[194] **1**	Qin (2000)[195] **1**
Armbrecht (1995)[196] **1**	Herzog (1985)[197] **6**	Racz (2002)[198] **1**
Armitage (1984)[199] **1**	Higuma (1994)[200] **1**	Radominski (1990)[141] **6**
Armitage (1985)[201] **1**	Hirobe (1995)[202] **1**	Rae (1994)[203] **1**
Armitage (1986)[204] **3**	Hisamichi (1990)[205] **3**	Rae (1998)[206] **1**
Armitage (1989)[207] **2**	Hiwatashi (1993)[208] **1**	Raine (1987)[209] **1**
Aroasio (1997)[210] **2**	Hiwatashi (2003)[211] **1**	Ramsey (2003)[212] **4**
Aste (1980)[213] **2**	Hoerr (1949)[214] **2**	Rasmussen (2003)[215] **3**
Bahrt (1984)[216] **1**	Hofbauer (1991)[217] **1**	Rattan (1986)[165] **7**
Baig (2001)[218] **1**	Hoff (2004)[219] **1**	Ratto (1992)[220] **2**
Baker (1988)[221] **6**	Hoffman (1983)[222] **1**	Reilly (1990)[223] **1**
Bampton (2002)[224] **1**	Honda (1995)[225] **1**	Rennert (2000)[226] **7**
Bampton (2004)[227] **1**	Hope (1996)[228] **2**	Rex (1991)[229] **1**
Barber (2002)[230] **2**	Howarth (2000)[231] **1**	Rex (1993)[232] **1**
Barbot (2004)[233] **4**	Humphrey (1969)[234] **6**	Ribet (1979)[235] **2**
Barnett (1952)[236] **2**	Imai (19790[237] **6**	Ribet (1980)[238] **2**
Barrison (1981)[239] **2**	Imperiale (2001)[240] **2**	Richardson (1977)[241] **1**
Barrison (1982)[242] **1**	Ishii (1990)[243] **1**	Riedel (1977)[244] **1**
Barrison (1985)[245] **1**	Ishikawa (1990)[246] **1**	Riegler (1990)[247] **1**
Bartnik (1982)[248] **1**	Isley (1981)[249] **1**	Robertsone (1987)[250] **4**
Bartnik (1986)[251] **2**	Ito (1990)[252] **1**	Robinson (1993)[253] **1**
Bassett (1980)[254] **2**	Iwase (1990)[255] **1**	Robinson (1994)[256] **1**
Bassil (1998)[257] **1**	Iwase (1995)[258] **2**	Robinson (1995)[259] **1**
Bat (1986)[260] **1**	Jacobi (1980)[261] **1**	Robra (1986)[262] **1**
Bech (1991)[263] **3**	Jankovic (1994)[264] **1**	Rochi (1982)[265] **1**
Bech (1992)[266] **3**	Jeanson (1994)[267] **2**	Rockey (1998)[268] **1**
Bedenne (1989)[269] **1**	Jensen (1986)[270] **1**	Ross (1976)[271] **1**
Bedenne (1990)[272] **1**	Jensen (1990)[273] **7**	Roth (1982)[274] **2**
Benesova (1993)[275] **2**	Jensen (1992)[276] **7**	Rozen (1980)[277] **2**
Benn (1981)[278] **6**	Jensen (1993)[279] **2**	Rozen (1986)[280] **7**
Bennett (4105)[281] **1**	Jensen (1994)[282] **2**	Rozen (1987)[283] **2**
Beretta (1978)[284] **1**	Jogensen (2001)[285] **3**	Rozen (1992)[286] **2**

Berry (1997)[287] **1**	John (1994)[288] **2**	Rozen (1995)[289] **2**
Bertario (1979)[290] **1**	Johne (2001)[291] **2**	Rozen (1997)[292] **2**
Bertario (1980)[293] **2**	Johnson (2002)[294] **2**	Rozen (1998)[295] **2**
Bertario (1999)[296] **1**	Jorge (1977)[297] **1**	Rozen (1999)[298] **2**
Besancon (1980)[299] **1**	Jorgensen (2002)[300] **7**	Rozen (1999)[301] **2**
Bhattacharya (1998)[302] **7**	Joseph (1988)[303] **1**	Rozen (2000)[304] **2**
Biedermann (1979)[305] **1**	Jouve (2001)[306] **3**	Ruiter (1978)[307] **1**
Bini (1999)[308] **1**	Kaneko (1984)[309] **2**	Saggioro (1987)[310] **1**
Bini (2000)[311] **1**	Kanzler (1978)[312] **2**	Saito (1984)[313] **2**
Birkner (2000)[314] **1**	Kapparis (1985)[315] **1**	Saito (1984)[316] **2**
Blazek (1976)[317] **2**	Kaye (1992)[318] **2**	Saito (1995)[319] **1**
Bond (1971)[320] **1**	Keller (2003)[321] **1**	Saito (2000)[322] **1**
Bond (1986)[323] **3**	Kemppainen (1994)[324] **2**	Saitoh (2000)[325] **2**
Bouvier (1999)[326] **3**	Kewenter (1984)[327] **1**	Sangster (1986)[328] **1**
Bouvier (2001)[329] **1**	Kewenter (1985)[330] **7**	Sasaki (1993)[331] **2**
Bradshaw (1995)[332] **6**	Kewenter (1986)[333] **1**	Sasaki (2001)[334] **1**
Bralow (1979)[335] **1**	Kewenter (1988)[336] **7**	Sato (1989)[337] **1**
Brandstatter (1978)[338] **1**	Kewenter (1989)[339] **1**	Sato (1989)[340] **1**
Brandstatter (1978)[341] **1**	Kewenter (1990)[342] **7**	Sato (1990)[343] **1**
Brault (1979)[344] **5**	Kewenter (1991)[345] **1**	Scales (2004)[346] **1**
Briancon (1985)[347] **1**	Kewenter (1994)[122] **1**	Scheida (1998)[348] **2**
Briancon (1987)[349] **1**	Kewenter (1994)[350] **1**	Scheitel (1999)[351] **1**
Brint (1993)[352] **1**	Kewenter (1995)[353] **1**	Schlucker (1999)[354] **1**
Britton (1984)[355] **1**	Kewenter (1996)[356] **1**	Schnell (1994)[357] **1**
Buchler (1994)[358] **1**	Khubchandani (1989)[359] **1**	Scholfield (2002)[360] **1**
Burany (1985)[361] **1**	Kida (1995)[362] **1**	Schuler (1979)[363] **2**
Burany (1989)[364] **1**	Kikkawa (1983)[365] **1**	Schwartz (1979)[366] **1**
Cailhol (2002)[367] **1**	Kim (1993)[368] **2**	Schwartz (1980)[369] **1**
Carlsson (1984)[370] **1**	Kim (2003)[371] **2**	Scriven (1989)[372] **6**
Castellanos (1994)[373] **2**	Kimmig (1989)[374] **2**	Segnan (2002)[375] **1**
Castiglione (1984)[376] **1**	Kita (1993)[377] **1**	Selby (1993)[378] **2**
Castiglione (1987)[379] **1**	Kitahara (1995)[380] **2**	Shah (1989)[381] **4**

Castiglione (1992)[382] **1**	Klaaborg (1986)[383] **1**	Shibata (1993)[384] **1**
Castiglione (1993)[385] **1**	Klug (1990)[386] **1**	Shida (1996)[387] **2**
Castiglione (1994)[388] **2**	Ko (2003)[389] **1**	Shields (2001)[390] **1**
Castiglione (1996)[391] **1**	Kobayashi (1980)[392] **1**	Shiwaku (1990)[393] **1**
Castiglione (2000)[394] **1**	Kobayashi (1982)[395] **1**	Siba (1980)[396] **1**
Castiglione (2002)[44] **3**	Kobayashi (1985)[397] **1**	Siba (1983)[398] **1**
Chambers (1980)[399] **1**	Kocna (2001)[400] **2**	Sieg (1998)[401] **1**
Champeau (1980)[402] **1**	Komuta (2000)[403] **2**	Sieg (1998)[404] **1**
Chang (1988)[405] **1**	Kronborg (1986)[406] **7**	Sieg (2002)[407] **1**
Chang (1997)[408] **6**	Kronborg (1986)[409] **7**	Singer (2002)[410] **3**
Chen (1993)[411] **1**	Kronborg (1987)[412] **7**	Slater (1985)[413] **1**
Chen (1996)[414] **2**	Kronborg (1989)[415] **3**	Slusser (1996)[416] **1**
Chen (2004)[417] **1**	Kronborg (1992)[418] **7**	Smith (2004)[419] **1**
Chiba (1990)[420] **2**	Kronborg (1996)[421] **3**	Sommer (1996)[422] **3**
Ciatto (2002)[423] **1**	Kronborg (1996)[424] **3**	Songster (1980)[425] **6**
Cohan (1993)[426] **1**	Kronborg (1997)[427] **3**	Songster (1980)[428] **2**
Cole (2001)[429] **1**	Kronborg (2002)[430] **2**	Sontag (1983)[431] **1**
Cole (2002)[432] **1**	Kronborg (2004)[433] **3**	Souques (2000)[434] **1**
Cole (2003)[435] **7**	Kruis (1979)[436] **2**	St John (1985)[437] **1**
Cole (2003)[43] **1**	Kruse (1982)[438] **1**	St John (1988)[439] **4**
Colin (1978)[440] **2**	Kumanishi (1989)[441] **1**	St John (1989)[442] **7**
Conen (1981)[443] **1**	Kunz (1976)[444] **1**	St John (1998)[445] **1**
Cortes-Ugalde (1992)[446] **1**	Kurnick (1980)[447] **1**	Steinberg (1981)[448] **1**
Coughlin (1987)[449] **2**	Kutter (1979)[450] **6**	Steinmetz (2001)[451] **1**
Courtier (2002)[452] **1**	Lallemand (1984)[453] **1**	Steinmetz (2003)[454] **1**
Crotta (2004)[455] **1**	Lamah (2001)[456] **2**	Stelling (1984)[457] **2**
Crowley (1983)[458] **2**	Lapointe (2003)[459] **4**	Stelling (1990)[460] **2**
Cruz-Correa (2004)[461] **2**	Larkin (1980)[462] **1**	Sterchi (1979)[463] **1**
Cummings (1984)[464] **1**	Launoy (1995)[465] **1**	Stewart (1979)[466] **1**
Cummings (1986)[467] **1**	Launoy (1996)[468] **1**	Stuart (1981)[469] **1**
Daron (1981)[470] **1**	Lawson (1982)[471] **1**	Stuart (1981)[472] **1**
Desai (1981)[473] **2**	Lazovich (1995)[474] **1**	Stuart (1982)[475] **1**

Deyhle (1976)[476] **2**	Lee (1983)[477] **1**	Suspiro (1997)[478] **2**
Di Cicco (1987)[479] **1**	Lee (1983)[480] **1**	Tada (1983)[481] **2**
Di Vincenzo (1989)[482] **1**	Leicester (1983)[483] **2**	Tadikonda (2000)[484] **1**
Donald (1972)[485] **6**	Leicester (1984)[486] **2**	Takagi (1993)[487] **1**
Durst (1976)[488] **1**	Letsou (1986)[489] **2**	Takahashi (1996)[490] **2**
Dvorak (2002)[491] **2**	Leu (1990)[492] **1**	Takaki (1995)[493] **6**
Dybdahl (1984)[494] **2**	Levenson (1993)[495] **1**	Takemasa (1998)[496] **2**
Ebener (1983)[497] **6**	Levin (1995)[498] **1**	Takeshita (1985)[499] **2**
Ebling (1989)[500] **1**	Levin (1997)[501] **1**	Tarraga (1999)[502] **1**
Eggertsen (1983)[503] **1**	Li (2003)[504] **1**	Tazi (1997)[505] **3**
Eliakim (1988)[506] **1**	Li (2004)[507] **1**	Tazi (1998)[508] **1**
Elliot (1984)[509] **1**	Lindholm (1995)[510] **1**	Tazi (1999)[511] **3**
Elliot (1984)[512] **1**	Lipshutz (1979)[513] **2**	Tazi (1999)[514] **3**
Escourou (1986)[515] **1**	Liu (2000)[516] **1**	Tellaroli (1981)[517] **1**
Evelegh (2000)[518] **2**	Lurie (1974)[519] **2**	Thomas (1990)[520] **1**
Faivre (1991)[521] **3**	Ma (2003)[522] **1**	Thomas (1992)[523] **3**
Faivre (1999)[524] **7**	Macaffe (2003)[525] **7**	Thomas (1995)[526] **1**
Faivre (1999)[527] **1**	Machicao (1999)[528] **1**	Thurber (1996)[529] **2**
Faivre (2004)[20] **1**	Mackett (1989)[530] **1**	Tibble (2001)[531] **2**
Faivre (2004)[532] **3**	Maercke (1980)[533] **2**	Tin (1993)[534] **1**
Farrands (1981)[535] **1**	Mahon (1994)[536] **2**	Tongeren (1982)[537] **1**
Fattah (1998)[538] **7**	Makisumi (1993)[539] **1**	Trojan (2002)[540] **2**
Faure (1998)[541] **4**	Mandel (1993)[542] **3**	Tsukamoto (1997)[543] **1**
Favennec (1992)[544] **1**	Mandel (1999)[545] **3**	Tsukioka (1995)[546] **2**
Feifel (1978)[547] **4**	Mandel (2000)[548] **7**	Tsumuraya (1989)[549] **2**
Feneyrou (1982)[550] **2**	Mangla (1981)[551] **1**	Turunen (1984)[142] **2**
Ferkl (1992)[552] **2**	Manus (1996)[553] **1**	Uhlig (1978)[554] **1**
Fernandez (1999)[555] **1**	Marchetto (1989)[556] **1**	Uhligh (1981)[557] **1**
Firouzi (1999)[558] **4**	Marjoram (1996)[559] **1**	Ujszaszy (1985)[560] **1**
Fischbach (1996)[561] **1**	Marks (1987)[562] **2**	UK CRC Screening Pilot Group (2004)[27] **1**
Fleisher (1977)[563] **6**	Marks (1997)[564] **1**	Unknown (1993)[565] **1**
Fleisher (1977)[566] **7**	Matlock (1979)[567] **2**	Vandenbroucke-Van der Wielen (1985)[568] **1**

Foliente (1995)[569] **2**	Maurer (1982)[570] **1**	Varro (1982)[571] **1**
Foll (1981)[572] **1**	Mazzarello (1990)[573] **1**	Verne (1993)[574] **1**
Foschi (1984)[575] **1**	McDonald (1983)[576] **1**	Verne (1998)[577] **1**
Frame (1982)[578] **1**	McGarrity (1989)[579] **1**	Villeneuve (2003)[580] **1**
Freedman (1994)[581] **1**	McGarrity (1990)[582] **1**	Wahrendorf (1993)[583] **1**
Frommer (1984)[584] **2**	Mehler (1969)[585] **6**	Walter (1991)[586] **1**
Frommer (1988)[587] **1**	Michalek (1982)[588] **1**	Wanebo (1986)[589] **1**
Fruhmorgen (1976)[590] **1**	Milkes (2003)[591] **1**	Warm (1977)[592] **2**
Fruhmorgen (1978)[593] **1**	Miller (1988)[594] **1**	Webendorfer (2004)[595] **1**
Fruhmorgen (1978)[596] **1**	Million (1982)[597] **1**	Wechselberger (1979)[598] **1**
Fruhmorgen (1980)[599] **1**	Mitsushima (1994)[600] **2**	Weiss (1977)[601] **2**
Fujita (1981)[602] **1**	Miyoshi (1995)[603] **2**	Weiss (1981)[604] **1**
Fujita (1984)[605] **1**	Moeller (1983)[606] **2**	Weller (1994)[607] **1**
Fujita (1986)[608] **1**	Monma (1992)[609] **1**	Wells (1980)[610] **2**
Fujita (1987)[611] **1**	Moran (1994)[612] **2**	Wexner (1984)[613] **2**
Fujiyoshi (1993)[614] **1**	Moreaux (1980)[615] **1**	Wielinger (1978)[616] **1**
Gabrielsson (1985)[617] **2**	Moriarty (1983)[618] **1**	Wilkes (1983)[619] **1**
Gallati (1978)[620] **6**	Morimoto (1990)[621] **1**	Williams (1985)[622] **2**
Giacchero (1982)[623] **2**	Morris (1974)[624] **6**	Willis (2004)[625] **1**
Gilbertsen (1980)[626] **1**	Morris (1982)[627] **1**	Winawar (1978)[628] **1**
Gilbertsen (1980)[629] **1**	Morris (1984)[630] **1**	Winawer (1977)[631] **1**
Glober (1974)[632] **1**	Morris (1991)[633] **1**	Winawer (1977)[634] **1**
Glober (1994)[635] **1**	Moss (1999)[636] **3**	Winawer (1977)[637] **7**
Gnauck (1974)[638] **1**	Murakami (1989)[639] **1**	Winawer (1978)[640] **1**
Gnauck (1977)[641] **5**	Murakami (2995)[642] **1**	Winawer (1979)[643] **1**
Gnauck (1978)[644] **1**	Murata (1994)[645] **1**	Winawer (1980)[646] **1**
Gnauck (1978)[647] **1**	Myers (2004)[648] **1**	Winawer (1991)[649] **2**
Gnauck (1979)[650] **1**	Nagaoka (1996)[651] **2**	Winawer (1993)[652] **2**
Gnauck (1980)[653] **1**	Nagasaka (1993)[654] **3**	Winchester (1980)[655] **1**
Gnauck (1980)[656] **1**	Nagasawa (1989)[657] **1**	Winchester (1983)[658] **1**
Gnauck (1982)[659] **1**	Nakajima (2002)[660] **2**	Wise (1994)[661] **2**
Gnauck (1983)[662] **1**	Nakajima (2003)[663] **1**	Withers (1978)[664] **1**

Gnauck (1983)[665] **1**	Nakama (1994)[666] **3**	Wong (2003)[667] **2**
Gnauck (1989)[668] **1**	Nakama (1996)[669] **1**	Wong (2003)[670] **2**
Gomez (1992)[671] **1**	Nakama (1996)[669] **2**	Wrobleski (1993)[672] **1**
Goodman (1977)[673] **1**	Nakama (1997)[674] **7**	Wu (2002)[675] **7**
Goodman (1978)[676] **1**	Nakama (1998)[677] **7**	Yamaguchi (1988)[678] **1**
Gopalswamy (1994)[679] **2**	Nakama (1999)[680] **1**	Yamamura (1993)[681] **2**
Goswitz (1987)[682] **1**	Nakama (1999)[683] **7**	Yaron (1986)[684] **1**
Goto (1988)[685] **1**	Nakama (2001)[686] **1**	Yoshida (1986)[687] **1**
Goumin (1991)[688] **1**	Nakama (2001)[689] **1**	Yoshii (1980)[690] **1**
Grazzini (2000)[691] **1**	Nakama (2001)[692] **7**	Yoshii (1981)[693] **2**
Grazzini (2004)[694] **1**	Nakama (2001)[695] **7**	Yoshii (1984)[696] **2**
Greegor (1967)[697] **2**	Nakama (2001)[698] **7**	Yoshinaga (1995)[699] **2**
Greegor (1969)[700] **1**	Ndjitoyap (1984)[701] **2**	Young (1986)[702] **6**
Greegor (1971)[703] **2**	Nichols (1986)[704] **1**	Young (1995)[705] **1**
Greegor (1972)[706] **2**	Nicolopoulos (1980)[707] **2**	Young (2001)[708] **1**
Greegor (1978)[709] **2**	Nicolopoulos (1980)[707] **5**	Young (2002)[710] **1**
Greegor (1980)[711] **1**	Nishikawa (1987)[712] **1**	Young (2003)[713] **2**
Greenberg (2000)[714] **2**	Niv (1990)[715] **1**	Zappa (1997)[716] **1**
Gregorio (1992)[717] **1**	Niv (1992)[718] **7**	Zappa (2001)[719] **1**
Griffith (1981)[720] **2**	Niv (1995)[721] **2**	Zarchy (1991)[722] **2**
Griffiths (1990)[723] **2**	Niv (1996)[724] **7**	Zhang (1992)[725] **2**
Gusi (1991)[726] **2**	Niv (1998)[727] **7**	Zhang (2001)[728] **1**
Habba (1983)[729] **1**	Nobuo (1993)[730] **1**	Zheng (1991)[731] **1**
Habr-Gama (1983)[732] **1**	Norfleet (1979)[733] **1**	Zheng (2003)[734] **1**
Hakkinen (1988)[735] **1**	Norfleet (1983)[736] **1**	Zhou (1994)[737] **1**
Hamajima (1990)[738] **2**	Norfleet (1986)[739] **2**	Zolenko (1985)[740] **1**
Hammes (1985)[741] **1**	Nozaki (2001)[742] **1**	Zoubek (1989)[743] **1**
Hammes (1987)[744] **1**	Odes (1992)[745] **1**	Zoubek (1989)[746] **1**
Han (1997)[747] **2**	Odom (2000)[748] **1**	Zoubek (1990)[749] **1**
Hardcastle (1980)[750] **1**	O'Donoghue (1984)[751] **1**	Zoubek (1990)[752] **1**
Hardcastle (1983)[753] **1**	Okamoto (1995)[754] **1**	

Table 26: Diagnostic accuracy studies, RCTs, and screening studies that were excluded from the review, and the reasons for their exclusion

Christensen (1974)[755] **8**	Three healthy children were tested with several FOBTs
Church (1997)[756] **8**	Estimating sensitivity from the Minnesota trial.
Fleisher (1991)[39] **8**	Samples with pre-established levels of hamoglobin
Klaaborg (1986)[757] **8**	Report in acceptability and ways to increase uptake
Lazovich (1994)[758] **8**	Type of FOBT was not specified in all cases
Nivatvongs (1981)[759] **8**	Only reported location of detected tumors
Ochiai (2002)[760] **8**	Testing response to animal haemoglobins
Robinson (1999)[761] **8**	Only reported interval cancers
Robinson (2000)[762] **8**	Only those who died were reviewed
Sack (1997)[763] **8**	Compliance only
Stroehlein (1976)[764] **8**	Evaluated effects of storage
Williams (1982)[765] **8**	Diagnostic case-controlled that used an inappropriate control group (people aged 20 to 82 years, with no confirmation of disease-free status)
Young (1996)[766] **8**	Investigated delay in sampling

The economic evaluations were excluded from the review for the following reasons:

1. Evaluated a single FOBT
2. Type of FOBT not specified
3. FOBT costed as part of an overall screening programme, not individually
4. FOBT combined with sigmoidoscopy
5. Not a full economic evaluation - either partial evaluation or only an abstract
6. Duplicate reports
7. Cost of work-up after a positive FOBT

Table 27: Economic evaluation studies that were excluded from the review, and the reasons for their exclusion

Allison (1985)[767] **1**	Helm (1998)[768] **5**	Robinson (1995)[769] **5**
Aguiar (1992)[770] **3**	Helm (1999)[771] **2**	Salkeld (1996)[772] **1**
Aguiar (2004)[773] **5**	Joseph (1987)[774] **6**	Sorrentino (1999)[775] **2**
Applegate (1979)[776] **1**	Joseph (1988)[777] **1**	Steele (2003)[778] **3**
Arveux (1992)[779] **1**	Khandker (2000)[780] **2**	Stone (2004)[781] **3**
Behney (1995)[782] **3**	Kristein (1980)[783] **1**	Theuer (2001)[784] **4**
Bretthauer (2002)[785] **4**	Lang (1994)[786] **1**	Tsuji (1991)[787] **1**
Brown (1990)[788] **1**	Lejeune (2003)[789] **1**	Vijan (2001)[790] **2**
Byers (1992)[791] **2**	Lejeune (2003)[792] **1**	Vilan (1997)[793] **6**
Canadian Coordinating Office for HTA (2002)[794] **2**		Wagner (1991)[795] **2**
Chang (1999)[796] **2**	Lejeune (2004)[797] **1**	Wagner (1996)[798] **1**
Cornell (1978)[799] **1**	Lieberman (1991)[800] **4**	Walker (1991)[801] **1**
Delco (1999)[802] **2**	Lieberman (1995)[803] **2**	Walker (1991)[804] **5**
Eddy (1984)[805] **1**	Lieberman (1995)[806] **2**	Walker (1993)[807] **6**
Eickhoff (2002)[808] **3**	Lieberman (1995)[809] **2**	Weller (1995)[810] **1**
Feldman (1981)[811] **6**	McGrath (2001)[812] **6**	Whynes (1992)[813] **1**
Frazier (2000)[814] **3**	McGrath (2002)[815] **7**	Whynes (1993)[816] **1**
Fric (1991)[817] **1**	McMahon (2001)[818] **2**	Whynes (1997)[819] **6**
Fric (1994)[820] **1**	Nakama (2000)[821] **1**	Whynes (1998)[822] **1**
Gow (1999)[823] **1**	Nakama (2001)[824] **1**	Whynes (1999)[825] **1**
Gyrd-Hansen (1998)[826] **1**	Neilson (1995)[827] **3**	Whynes (2004)[828] **1**
Gyrd-Hansen (1998)[829] **1**	Neuhauser (1975)[830] **1**	Yamamoto (2000)[831] **1**
Helm (1997)[832] **6**	O'Leary (2004)[833] **2**	Yoshinaga (1997)[834] **1**
Helm (1997)[835] **6**	Parson (2000)[836] **1**	Zauber (2003)[837] **6**

APPENDIX I: DATABASES ON WHICH INCLUDED STUDIES WERE LOCATED

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
10	Sung	2003	X	X	X	X	X			X							
37	Berchi	2004	X	X			X										
64	Liu	2003	X	X	X	X	X										
108	Gondal	2003	X	X	X	X	X	X									
160	Cheng	2002	X	X			X										
220	Chen	2002	X	X	X	X	X										
231	Parker	2002	X	X			X	X									
232	Zhang	2002	X	X	X	X	X										
259	Niv	2002	X	X	X	X	X	X									
275	Rennert	2001	X	X	X	X	X										
296	Lieberman	2001	X	X	X	X	X										
309	Parikh	2001	X	X	X	X	X										
324	Nakama	2001	X	X			X										

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
355	Nakama	2000	X		X	X	X										
360	Nakama	2000	X			X	X	X									
367	Nakama	2000	X	X		X	X										
416	Nakama	2000	X	X	X	X	X										
495	Rasmussen	1999	X	X	X	X	X	X									
609	Brevinge	1997	X	X	X	X	X	X									
614	Castiglione	1997	X	X					X	X							
618	Launoy	1997	X	X	X	X	X										
636	Nakama	1997	X	X	X		X	X									
657	Lindholm	1997	X	X	X	X	X	X									
682	Nakama	1996	X														
697	Itoh	1996	X							X							
698	Nakama	1996	X														
720	Robinson	1996	X	X			X										

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
737	Allison	1996	X	X	X	X	X		X								
741	Li	1995	X	X	X												
834	Nakama	1994	X	X	X		X										
837	Shimbo	1994	X	X		X			X								
871	Zhou	1993	X		X		X										
884	Fujiyoshi	1993	X	X	X												
924	St John	1993	X	X	X	X											
975	St John	1992	X	X		X	X										
994	Murakami	1992	X	X		X	X										
1005	Miyoshi	1992	X	X		X	X										
1044	Castiglione	1991	X	X			X										
1073	Mant	1990	X					X									
1142	Allison	1990	X	X		X	X										
1179	Mandel	1989	X	X		X	X	X									

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
1232	Zhu	1988	X	X			X										
1250	Michalek	1988	X														
1282	Kikkawa	1987	X														
1338	Bang	1986	X	X			X										
1545	Uhlig	1981	X	X													
2411	Takeshita	1985		X													
2428	Takeshita	1982		X													
2506	Morikawa	2004					X										
2507	Lim	2004					X										
2663	Levin	2000			X		X										
2731	Kim	1998			X		X										
2778	Bhattacharya	1997			X		X										
2780	Okamoto	1997			X		X										
2783	Russo	1997			X		X										

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
2818	Bennett	1996			X		X										
3007	Foley	1992				X	X										
3045	Walker	1992					X										
3374	Griffiths	2003			X												
3796	Arveux	1998				X											
4097	Chen	1997									X						
4121	Ribet	1980						X									
4127	Ballegooijen	2003															X
4175	Collins	2004					X										
4205	Nakama	2004	X	X	X	X	X										
4237	Wong	2004	X*														
4258	Tada	1986									X						
4260	Zhou	1987									X						
4288	Flehinger	1988									X						

EndNote Study ID:	First Author:	Year:	Medline	Embase	BIOSIS	Pascal	SCI	Central	HEED	NHS EED	Handsearching Bibliographies	Handsearching Journal	CDSR	DARE	Internet	LILACS	HTA
4378	Klug	1983									X						
4384	Lampe	1982									X						
4452	Winawer	1980									X						
4453	Tada	1988									X						
4455	Miyoshi	1988									X						
4456	Matsuse	1989									X						
4460	Kawai	1987									X						

APPENDIX J: QUADAS ITEMS FOR EACH INCLUDED STUDY

Table 28: Results of the quality assessment for included FOBT studies. Studies scored Yes (Y), No (N) or Unclear (UC) for each quality item

	1. Spectrum composition	2. Selection criteria	3a. Appropriate reference standard - positive FOBT/cases	3b. Appropriate reference standard - neagative FOBT/controls	4. Partial verification bias	5. Differential verification bias	6a. Index test execution details	6b. Reference standard execution details	7a. Test review bias	7b. Diagnostic review bias	8. Clincial review bias	9. Uninterpretable/intermediate results	10. Withdrawals
Allison (1996)[8]	Y	Y	Y	N	Y	N	Y	N	Y	UC	UC	Y	N
Allison (1990)[64]	Y	Y	Y	N	Y	N	Y	N	UC	UC	UC	Y	Y
Allison (2002)[5]	UC	N	Y	N	Y	N	N	Y	UC	UC	UC	Y	Y
Bang (1986)[65]	N	N	Y	N	Y	N	Y	Y	UC	UC	UC	Y	Y
Bennett (1996)[93]	UC	N	N	N	Y	Y	N	N	UC	UC	UC	N	N
Bhattacharya (1997)[81]	UC	N	Y	Y	Y	Y	N	N	Y	N	N	UC	Y
Brevinge (1997)[107]	Y	Y	N	N	Y	Y	N	Y	UC	UC	UC	Y	Y
Castiglione (1991)[94]	Y	Y	N	N	Y	N	N	N	Y	N	UC	Y	N
Chen (2002)[66]	Y	Y	Y	Y	Y	Y	N	N	UC	UC	UC	Y	Y
Chen (1997)[95]	Y	N	N	N	Y	N	N	N	UC	UC	UC	N	N
Cheng (2002)[96]	Y	Y	Y	Y	Y	Y	N	N	UC	UC	UC	Y	Y
Collins (2005)[97]	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	UC	Y	Y
Foley (1992)[67]	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gondal (2003)[108]	Y	Y	Y	N	Y	N	N	Y	UC	UC	UC	Y	Y
Itoh (1996)[98]	Y	Y	Y	Y	Y	N	Y	N	UC	UC	UC	Y	Y
Kawai (1987)[82]	N	N	Y	Y	Y	Y	Y	Y	UC	Y	N	Y	Y
Kikkawa (1987)[6]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Kim (1998)[99]	UC	N	N	N	Y	Y	N	N	UC	UC	UC	Y	Y
Klug (1983)[68]	UC	N	N	N	Y	N	Y	N	UC	N	UC	Y	Y
Lampe (1982)[83]	N	Y	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Launoy (1997)[69]	Y	N	Y	N	Y	N	N	N	UC	UC	UC	N	Y
Li (1995)[84]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Lieberman (2001)[70]	Y	Y	Y	N	Y	N	N	N	Y	Y	UC	Y	Y

	1. Spectrum composition	2. Selection criteria	3a. Appropriate reference standard - positive FOBT/cases	3b. Appropriate reference standard - neagative FOBT/controls	4. Partial verification bias	5. Differential verification bias	6a. Index test execution details	6b. Reference standard execution details	7a. Test review bias	7b. Diagnostic review bias	8. Clincial review bias	9. Uninterpretable/intermediate results	10. Withdrawals
Liu (2003)[71]	Y	Y	Y	Y	Y	Y	N	N	Y	UC	UC	Y	Y
Mandel (1989)[110]	Y	N	Y	N	Y	N	N	N	UC	UC	UC	N	Y
Matsuse (1989)[2]	N	N	Y	Y	Y	Y	N	Y	UC	Y	N	Y	Y
Michalek (1988)[100]	Y	N	N	N	Y	Y	N	Y	Y	UC	UC	Y	Y
Miyoshi (1992)[9]	N	Y	Y	N	Y	UC	Y	Y	UC	Y	UC	N	N
Miyoshi (1988)[1]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Morikawa (2004)[101]	UC	N	Y	Y	Y	Y	N	N	UC	UC	UC	Y	Y
Murakami (1992)[72]	UC	N	N	N	Y	Y	N	N	UC	UC	UC	Y	Y
Nakama (2001)[73]	Y	Y	Y	Y	Y	Y	Y	N	UC	UC	UC	Y	Y
Nakama (2000)[74]	Y	Y	Y	Y	Y	Y	Y	N	UC	UC	UC	Y	Y
Nakama (2000)[75]	UC	N	Y	Y	Y	Y	N	N	UC	UC	UC	Y	Y
Nakama (2000)[76]	UC	Y	Y	Y	Y	Y	Y	N	UC	UC	UC	Y	Y
Nakama (2000)[42]	N	N	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y
Nakama (1997)[86]	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	UC	UC
Nakama (1996)[87]	N	N	Y	Y	Y	Y	N	N	UC	Y	UC	Y	Y
Nakama (1996)[102]	N	N	Y	N	Y	N	Y	N	UC	UC	UC	Y	N
Nakama (1994)[7]	N	N	Y	Y	Y	Y	Y	Y	UC	Y	UC	Y	Y
Nakama (2004)[85]	N	N	Y	Y	Y	Y	Y	Y	UC	Y	UC	UC	UC
Niv (2002)[112]	Y	Y	Y	N	Y	N	N	N	Y	UC	UC	Y	Y
Okamoto (1997)[103]	UC	N	Y	Y	Y	Y	N	N	UC	UC	UC	Y	Y
Parikh (2001)[77]	Y	Y	Y	N	Y	N	Y	N	Y	N	UC	Y	Y
Rasmussen (1999)[113]	UC	N	Y	N	Y	N	N	N	Y	Y	UC	Y	Y
Rennert (2001)[105]	Y	N	Y	N	Y	N	N	N	UC	UC	UC	Y	Y
Ribet (1980)[78]	N	N	UC	UC	Y	N	N	N	Y	UC	UC	Y	Y
St John (1993)[10]	N	Y	Y	UC	UC	Y	Y	N	Y	UC	N	Y	Y
St John (1992)[79]	N	Y	Y	UC	UC	Y	Y	N	N	Y	UC	Y	Y

	1. Spectrum composition	2. Selection criteria	3a. Appropriate reference standard - positive FOBT/cases	3b. Appropriate reference standard - neagative FOBT/controls	4. Partial verification bias	5. Differential verification bias	6a. Index test execution details	6b. Reference standard execution details	7a. Test review bias	7b. Diagnostic review bias	8. Clincial review bias	9. Uninterpretable/intermediate results	10. Withdrawals
Sung (2003)[80]	Y	Y	Y	Y	Y	Y	N	Y	Y	UC	UC	Y	Y
Tada (1986)[88]	N	N	Y	Y	Y	Y	Y	Y	UC	Y	N	Y	Y
Tada (1988)[89]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Takeshita (1985)[4]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Takeshita (1982)[3]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Winawer (1980)[106]	UC	N	N	N	Y	Y	N	N	UC	UC	UC	UC	Y
Zhang (2002)[90]	N	Y	Y	Y	Y	Y	N	Y	UC	Y	UC	Y	Y
Zhou (1993)[46]	UC	N	Y	UC	Y	N	Y	N	UC	UC	UC	Y	Y
Zhou (1987)[91]	N	N	UC	UC	UC	UC	N	N	UC	Y	N	Y	Y
Zhu (1988)[92]	N	N	UC	UC	UC	UC	Y	N	UC	UC	N	UC	UC

APPENDIX K: PROTOCOL CHANGES

Inclusion criteria

Population

We initially intended to include only studies of average-risk populations above the age of 50 years (the likely target of any UK screening programme). The age of the population selected in the identified studies varied with design (case-controls and cohort studies) and location. It was therefore decided to expand the inclusion criteria so that all studies that included an adult, average-risk population, preferentially invited for screening for colorectal neoplasms were included.

Existing systematic reviews

It was decided not to include existing systematic reviews in the current review but instead to use these as sources of potentially relevant studies. This was due to differences between the identified systematic reviews and the proposed inclusion criteria and methods of analysis for the current review.

APPENDIX L: CRD STRUCTURED SUMMARIES OF THE INCLUDED ECONOMIC EVALUATIONS

CASTIGLIONE (1997) [117]

Cost analysis in a population based screening programme for colorectal cancer: comparison of immunochemical and guaiac faecal occult blood testing.
Castiglione G, Zappa M, Grazzini G, Sani C, Mazzotta A, Mantellini P, Ciatto S.
Journal of Medical Screening, 1997;4(3):142-6.

Two faecal occult blood tests (FOBT) for colorectal cancer screening: Haemoccult (guaiac based) and reversed passive haemagglutination (RPHA) tests. RPHA tests were interpreted according to two different positivity thresholds.

Disease: Neoplasms

Type of intervention: Screening

Hypothesis/study question:
To evaluate the costs of one day reversed passive haemagglutination (RPHA) testing and three-day rehydrated guaiac testing in the same population. RPHA was clearly stated by the authors as a comparator. These screening procedures have been used in screening programmes that were effective in reducing colorectal cancer mortality, but each is associated with a different sensitivity and specificity level that is likely to affect the size of the protective effect of screening and costs.

Economic study type: Cost-effectiveness analysis.

Study population: Subjects aged 40-70 years.

Setting
Hospital. Six municipalities in the province of Florence, Italy were involved in the screening. The economic study was carried out in Italy.

Dates to which data relate
Subjects were recruited into the study during the period March 1992 to September 1995. 1996 costs were used for the assessment phase. The year for the remainder of the prices used in the analysis was not stated.

Source of effectiveness data
The evidence for final outcomes was derived from a single study.

Links between effectiveness and cost data
The costing was based on the same patient sample as that used in the effectiveness analysis, and appears to have been carried out retrospectively.

Single Study
Study sample
Power calculations were not used to determine the sample size. Subjects living in the six municipalities in the province of Florence (28,282 inhabitants aged 40-70) were enrolled in the study and underwent a double FOBT screening investigation. 8,353 subjects were recruited (3,887 men, mean age 54.2, 2,509 over the age of 49; 4.466 women, mean age 54.3, 2,906 older than 49). Screening with the double FOBT protocol was repeated after two years only in two of the six municipalities (7,982 subjects, aged 40-70). Overall mean compliance in the course of the study was 38.7%.

Study design
The study was a prospective case-series which enrolled the population of six municipalities in the province of Florence, Italy.

Analysis of effectiveness
The primary health outcome used in the analysis was the number of cancers/adenomas detected by the respective tests.

Effectiveness results
Haemoccult, RPHA positive (+) and borderline (+/-), and RPHA (+ only) detected 16, 22 and 18 cancers and 124, 105 and 181 adenomas respectively. All of the 13 Dukes's A carcinomas were detected by RPHA (+ and +/-). Haemoccult and RPHA (+) detected six and nine Dukes's A cancers respectively. Curative polipectomy with no need for further surgery was obtained in two patients with a positive Haemoccult test, and in six with a positive (+) RPHA test. Three cancers were detected at repeat screening. All of them were Haemoccult negative; two were RPHA(+); one was RPHA (+/-).

Clinical conclusions
RPHA (+ and +/-) showed the highest and RPHA (+ only) the lowest positivity rate at first screening. The Haemoccult positivity rate was highest at repeat screening. The authors concluded that screening by RPHA had higher efficacy in reducing CRC mortality and incidence.

Economic analysis
Measure of benefits used in the economic analysis
The measure of benefits used in the economic analysis was the number of cancers/adenomas detected by the respective tests. screening programme was costed: recruitment, screening and assessment. For the first two phases all relevant resources consumed by the programme were listed and measured. For staff costs the resource percentage attributable to the screening programme was apportioned. General expenses were calculated by dividing the total expense of the centre by the percentage of the total area currently occupied by the FOBT programme. The cost of the building was based on market rental prices. Costs for the recruitment phase included the resources for general organisation and direction of the programme. To calculate the costs for the assessment phase, National Tariffs for 1996 were used. The year for the rest of the prices was not stated. Resource quantities were not reported separately from the prices.

Indirect costs: Not included

Currency
US dollars ($), converted from Italian lira at an exchange rate of $1 to 1,550 Italian lira.

Sensitivity analysis
In a sensitivity analysis an additional evaluation of the costs of the assessment phase was made according to the estimates of the mean costs of endoscopic examinations and treatments carried out by a working group.

Estimated benefits used in the economic analysis
Haemoccult, RPHA positive (+) and borderline (+/-), and RPHA (+ only) detected 16, 22 and 18 cancers and 124, 105 and 181 adenomas respectively. All of the 13 Dukes's A carcinomas were detected by RPHA (+ and +/-). Haemoccult and RPHA (+) detected six and nine Dukes's A cancers respectively. Three cancers were detected at repeat screening. All of them were Haemoccult negative; two were RPHA(+); one was RPHA (+/-).

Cost results
At the first screening round RPHA (+ and +/-) was the most costly ($136,120 per 10,000 screened subjects with 38.7% attendance rate) as the higher recall rate resulted in the highest cost for the assessment phase. RPHA (+) was the least expensive test in all programme phases ($96,770). Haemoccult was in an intermediate position for total and assessment costs but was the most costly test for the screening phase (total cost was $120,640). At repeat screening and in subjects aged 40-49 the total costs were lower than at the first screening owing to the lower positivity and recall rate. At first screening RPHA (+ and +/-) had the highest cost for each screened subject ($35.1) and RPHA (+) the lowest ($25).

Synthesis of costs and benefits
Haemoccult showed the highest costs for each subject with detected cancer or adenomas ($12,900). RPHA(+) had the lowest cost for detected cancer ($9,020), whereas RPHA (+ and +/-) had the lowest cost for each subject with adenoma(s) ($1,780). Costs for each subject screened decreased at the second round ($25.1) or in younger subjects ($20.6 - $27.1). The cost for each subject with cancer or adenoma(s), however, increased at the second round ($18,990 and $3,450 respectively) and for younger subjects. When the working group's cost estimates were used, rather than ministerial tariffs, the overall assessment costs at first screening were increased by about 25%. When the working group's cost estimates for endoscopic costs were considered instead of national tariffs, costs for each screened subject, or for each subject with detected cancer or adenoma(s), increased by 16% for Haemoccult, by 17% for RPHA (+ and +/-), or 10% for RPHA (+), in subjects aged 50-70 at first screening. The group's estimates of assessment costs caused smaller increases of costs at first screening in subjects aged 40-49 and an increase of 11% at repeat screening. With higher compliance rates, costs for each screened subject or each detected cancer or adenoma(s) would be lower, though a great improvement in compliance would be needed to lower total costs markedly.

Conclusions, commentary and implications
Authors' conclusions
Screening for colorectal cancer by an immunochemical FOBT based on RPHA is more cost effective than guaiac testing. Further efforts should be concentrated on the evaluation of RPHA sensitivity for colorectal cancer to assess the optimal positivity threshold. The analysis confirmed that screening for colorectal cancer under the age of 50 is not cost-effective.

CRD commentary
Selection of comparators: A justification was given for the comparators used: all of the alternative screening procedures have been used in screening programmes that were effective in reducing colorectal cancer mortality. You should consider whether these are widely used health technologies in your own setting. Validity of estimate of measure of benefit: The estimate of the measure of benefit used in the economic analysis is likely to be internally valid. Validity of estimate of costs: Resource quantities were not reported separately from the prices but adequate details of cost estimation were given. Other issues: The issue of generalisability to other settings or countries was not addressed.

WALKER (1992) [115]

Filtering strategies in mass population screening for colorectal cancer: an economic evaluation

Walker A, Whynes D K. Medical Decision Making 1992;12:2-7

Health technology
The use of mass population filtering strategies for the selection of individuals requiring further screening (colonoscopic investigation) for the detection of colorectal cancer (CRC). The strategies examined were as follows

Strategy 1: the Haemoccult faecal occult blood (FOB) test. A 3-day test, with no subsequent retesting of positives or negatives.

Strategy 2: the Haemoccult FOB test. All first-round positive results are subjected to a retest and confirmed positives proceed to investigation.

Strategy 3: the Haemoccult FOB test. All first-round positive results are subjected to a retest and confirmed positives proceed to investigation. Negative retests take a third test and those confirmed positive proceed to investigation.

Strategy 4: the Haemoccult FOB test as in strategy 1, but all test samples are rehydrated prior to development. All positives proceed to investigation.

Strategy 5: the Haemoccult FOB test as in strategy 1, but administered over 6 days and no retesting.
Strategy 6: the Hemeselect FOB test.

Strategies 7, 8 and 9 used Hemoquant FOB tests with different sensitivities. Strategy 7 was sensitive at 1.5 mg haemoglobin-g stool, strategy 8 was sensitive at 2.0 mg/g, and strategy 9 was sensitive at 3.0 mg/g.

Strategy 10: the Fecatwin/Feca EIA FOB test.

Strategy 11: the Coloscreen FOB test.

Strategy 12: the Ez-Detect FOB test.

Strategy 13: a risk questionnaire in which positives are identified on the basis of the presence of one or more risk factors, such as symptoms, personal risk, or familial risk.

Strategy 14: no screening.

Disease: Neoplasms; Digestive system diseases.

Type of intervention: Screening.

Hypothesis/study question
The objective of the study was to assess the cost-effectiveness of the alternative mass population filtering strategies for the screening of CRC in comparison with no screening (strategy 14) in the UK. The use of pre-diagnostic techniques was advocated, not only to increase patient compliance (which was low with more invasive procedures) but also to reduce the costs (which increased when more accurate techniques were selected). The perspective adopted in the study was unclear, but it might have been that of the UK National Health Service (NHS).

Economic study type: Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 100,000 asymptomatic individuals. In general, persons over 50 years of age were included in the target population.

Setting
Although not explicitly stated, the setting might have been primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence came from studies published from 1987 to 1991. The cost data were estimated from an article published in 1989. The price year was 1989.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies, supplemented by authors' assumptions.

Modelling
A traditional economic modelling approach appears to have been used to assess the costs and benefits of the filtering strategies. Decision trees were not used.

Review/synthesis of previously published studies

Outcomes assessed in the review
The outcomes assessed from the literature were the compliance rates and sensitivity and specificity values.

Study designs and other criteria for inclusion in the review
It was unclear whether a formal review of the literature was undertaken, but most of the evidence came from randomised clinical trials.

Sources searched to identify primary studies: Not stated.

Criteria used to ensure the validity of primary studies: Not stated.

Methods used to judge relevance and validity, and for extracting data: Not stated.

Number of primary studies included
Ten primary studies provided the evidence.

Method of combination of primary studies
The authors did not report the method used to combine the results of the individual studies, although a narrative method appears to have been used.

Investigation of differences between studies: Not stated.

Results of the review

The compliance rate was 57.8% for strategies 1 to 4 and 6 to 10, 53.4% for strategy 5, 86% for strategy 11, 88% for strategy 12, and 69% for strategy 13.

The sensitivities and specificities of the strategies were as follows:

- *Strategy 1*, sensitivity 0.67 and specificity 0.97
- *Strategy 2*, sensitivity 0.58 and specificity 0.99
- *Strategy 3*, sensitivity 0.65 and specificity 0.99
- *Strategy 4*, sensitivity 0.72 and specificity 0.95
- *Strategy 5*, sensitivity 0.74 and specificity 0.99
- *Strategy 6*, sensitivity 0.95 and specificity 0.93
- *Strategy 7*, sensitivity 0.90 and specificity 0.94
- *Strategy 8*, sensitivity 0.85 and specificity 0.95
- *Strategy 9*, sensitivity 0.70 and specificity 0.98
- *Strategy 10*, sensitivity 0.67 and specificity 0.91

- *Strategy 11*, sensitivity 0.33 and specificity 0.94
- *Strategy 12*, sensitivity 0.36 and specificity 0.89
- *Strategy 13*, sensitivity 0.70 and specificity 0.81

Estimates of effectiveness based on opinion

Methods used to derive estimates of effectiveness
The authors formulated several assumptions to derive some estimates of effectiveness.

Estimates of effectiveness and key assumptions
It was estimated that the prevalence of CRC was 3.5 per thousand. The compliance rates of some filtering procedures were not available from the literature and were assumed to have been comparable with the rates of other similar procedures (reported above).

Economic analysis

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of cancers detected with each filtering strategy in a target population of 100,000. The number of positives was also reported.

Direct costs
The cost analysis was based on the results of a published clinical trial, which was partly used as source of evidence (Hardcastle et al., see Other Publications of Related Interest). Limited information on the economic analysis was provided. The unit costs and the quantities of resources used were not analysed separately. The health services included in the economic evaluation were filtering tests and colonoscopic investigation. The cost/resource boundary of the study was unclear. The only unit cost reported was that of colonoscopy. Discounting does not appear to have been relevant as the costs were incurred during a short timeframe. The resource use data were mainly derived from authors' assumptions. It was also assumed that the relevant filter was distributed to all members of the target population, and that all unused material was discarded. The price year was 1989.

Indirect costs
The indirect costs were not included in the economic evaluation.

Currency
UK pounds sterling (£). The authors stated that when the article was written, the pound was equivalent to approximately 2 US dollars.

Statistical analysis of costs
The costs were treated deterministically.

Sensitivity analysis
One- and two-way sensitivity analyses were carried out to assess the impact on the estimated cost-effectiveness ratios of varying the compliance rate and the prevalence rate. The ranges used were derived from authors' opinions.

Estimated benefits used in the economic analysis
The number of cancers detected in a target population of 100,000 was:
135 with strategy 1, 118 with strategy 2, 131 with strategy 3, 145 with strategy 4, 137 with strategy 5, 192 with strategy 6, 182 with strategy 7, 172 with strategy 8, 142 with strategy 9, 136 with strategy 10, 99 with strategy 11, 112 with strategy 12, 169 with strategy 13, and 0 with strategy 14.

Cost results
The estimated total costs (in million) in a target population of 100,000 with each strategy were:

Strategy 1, £0.38
Strategy 2, £0.26
Strategy 3, £0.28
Strategy 4, £0.50
Strategy 5, £0.43
Strategy 6, £1.03
Strategy 7, £1.88

Strategy 8, £1.82
Strategy 9, £1.64
Strategy 10, £0.86
Strategy 11, £0.66
Strategy 12, £1.11
Strategy 13, £1.45
Strategy 14, £0.

Synthesis of costs and benefits
An average cost-effectiveness ratio was calculated to combine the costs and benefits of the filtering strategies. After dominated strategies were eliminated, the incremental cost-effectiveness ratios of the remaining strategies were calculated.

The average cost per cancer detected with each strategy was:
Strategy 1, £2,814
Strategy 2, £2,202
Strategy 3, £2,116
Strategy 4, £3,456
Strategy 5, £3,156
Strategy 6, £5,356
Strategy 7, £10,323
Strategy 8, £10,569
Strategy 9, £11,561
Strategy 10, £6,373
Strategy 11, £6,691
Strategy 12, £9,869
Strategy 14, £8,582

The incremental cost per cancer saved was £2,116 with strategy 3 over strategy 14, and £12,376 with strategy 6 over strategy 3.

The authors noted that the choice of the preferred approach depended on the financial value the decision-maker put on a case of cancer missed. The sensitivity analysis revealed that variations in the model assumptions did not alter the ranking of the filtering tests, although the cancer-miss valuations increased with higher prevalence and lowered with higher compliance rates (range: £1,900 - £4,800).

Conclusions, commentary and implications

Author's Conclusions
The Hemeselect 3-day faecal occult blood (FOB) test and Haemoccult 3-day FOB test with two retests were the most cost-effective strategies of all those investigated. However, the choice of the filtering screening depended on the payer's willingness to pay for a case of missed cancer. Under some scenarios, the no screening option could have been the preferred strategy.

CRD commentary

Selection of comparators:
The choice of the comparators appears to have been appropriate, as it covered all possible filtering strategies used for the detection of CRC in asymptomatic individuals. The authors provided a justification for the selection of the interventions under evaluation. The no screening option was also appropriately considered. You should decide whether these are valid comparators in your own setting.

Validity of estimate of measure of effectiveness:
The authors did not state that a systematic review of the literature had been undertaken. The methods used to find and select the primary studies were unclear, therefore some relevant studies could have been excluded. Although most of the effectiveness estimators were derived from clinical trials, the quality and validity of the data collected from these studies was not reported. The primary estimates were combined using narrative methods. The authors made several assumptions to derive some of the effectiveness estimators, which were then varied in the sensitivity analysis. However, the impact of variations in estimates derived from the literature was not investigated. The authors noted that comparing data derived from different sources was a problem, and some data could have been biased. Further, the published evidence pertaining to the risk questionnaire was controversial, which added further uncertainty to the results of the study.

Validity of estimate of measure of benefit:
The summary benefit measure was specific to the interventions considered in the study and would be difficult to compare with the benefits of other health care interventions. The use of life-years saved as a result of the filtering strategies would have been helpful, but the authors stated that such an estimate would have needed epidemiological data that they did not possess.

Validity of estimate of costs:
The authors did not state explicitly the perspective of the study, although it might have reflected that of the NHS. However, only the costs strictly related to the implementation of the filtering strategies were considered. The authors acknowledged that the inclusion of cancer treatment costs would have been more appropriate. The price year was reported, which will simplify reflation exercises in other settings. However, there was limited information on the whole cost analysis since the data were derived from a published study. The unit costs were not reported separately from the quantities of resources used, and it may therefore be difficult to replicate the study. Most of the resource use data were derived from authors' assumptions. The costs were treated deterministically, and were specific to the study setting as no sensitivity analyses were carried out.

Other issues:
The authors did not make extensive comparisons of their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. However, some sensitivity analyses were carried out on key estimates, and the results would appear to be applicable to settings with difference compliance and cancer prevalence rates. The study referred to the general population of asymptomatic individuals and this was reflected in the conclusions of the analysis. The authors noted some limitations to the validity of their analysis, which mainly related to the source of the clinical data.

Implications of the study
The authors stated that their results relied on the current state of clinical research and that they may require revision as this research progresses.

SHIMBO (1994) [119]

Cost-effectiveness analysis of strategies for colorectal cancer screening in Japan.
Shimbo T, Glick H A, Eisenberg J M. International Journal of Technology Assessment in Health Care 1994;10(3):359-375.

Health technology
Several screening strategies for colorectal cancer (CRC) were examined. These were based on the combination of biochemical faecal occult blood testing (F), immunological faecal occult blood testing (IF), barium enema (B), colonoscopy (C) and sigmoidoscopy (S). The strategies were as follows.

Strategy 1 was F-F-B-C. F was performed annually, followed by second F if the first results were positive. The patient underwent a B if the second test result was positive and C if the B result was positive.

Strategy 2 was IF2y-C. IF was performed every 2 years and, if positive, was followed by C.

S*trategy 3* was F-C. F was performed annually and, if positive, was followed by C.

Strategy 4 was IF-B-C. IF was performed annually and, if positive, was followed by a B. If the B was suggestive of cancer beyond the range of S, the patients underwent C, while if the B was suspicious within range, then S was conducted.

Strategy 5 was IF-B/S-C. This was similar to strategy 4, but both a B and S were performed after a positive IF result. If S revealed a lesion, then examination was stopped. If S was negative but the B was positive, C was performed.

Strategy 6 was IF-C. IF was performed annually and, if positive, was followed by C.

Strategy 7 was IF/S3y-C. IF was performed annually and, if positive, was followed by C. In addition, S was performed every 3 years and, if positive, was followed by C.

Strategy 8 was no screening.

Disease: Neoplasms; Digestive system diseases.

Type of intervention: Screening.

Hypothesis/study question
The objective of the study was to assess the cost-effectiveness of the alternative mass screening strategies for the detection of CRC in Japan. The no screening option (strategy 8) was also considered as the basic comparator. The analysis also investigated the optimal age at which screening should begin, and the impact of compliance on the test results. The perspective of the payer was adopted in the study.

Economic study type: Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of asymptomatic 40-year-old Japanese men and women. Other starting ages were also considered.

Setting
The setting appears to have been primary care. The economic study was conducted in Japan.

Dates to which data relate
The effectiveness data were derived from studies published between 1975 and 1990. No dates for the resource use data were explicitly reported. The costs were, in part, obtained from studies published in 1989 and 1990. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A state-transition model was constructed to simulate the natural history of CRC in a cohort of 100,000 asymptomatic men and women in Japan. The model was populated mainly with published data specific to the Japanese setting. Individuals were followed for 35 years. The cycle length appears to have been one year. Six different health states were considered. These were cancer-free and polyp-free, polyp remains benign, polyps transforms into cancer, CRC, follow-up after cancer treatment, and death.

Review/synthesis of previously published studies
Outcomes assessed in the review
The outcomes derived from the literature were the sensitivity and specificity of the alternative screening tests, the complication rates, and other probability values used in the decision model.

Study designs and other criteria for inclusion in the review
It was not stated whether a formal review of the literature was undertaken and the design of the primary studies was unclear. The stage- and age-specific distribution of undetected cancers and estimated detection rates were derived from observational data in a Japanese regional cancer registry. The probabilities of death were derived from Japanese life tables. Only those studies that specified clinical data were considered.

Sources searched to identify primary studies: Not stated.

Criteria used to ensure the validity of primary studies: Not stated.

Methods used to judge relevance and validity, and for extracting data: Not stated.

Number of primary studies included
Forty primary studies provided the evidence.

Method of combination of primary studies
The primary studies appear to have been combined using narrative methods. The 95% confidence interval (CI) was derived from the sum of total cases using the method of Blyth and Still. Ranges (minimum and maximum) were also reported when the data were derived from more than two studies.

Investigation of differences between studies: Not stated.

Results of the review
The specificity of F was 0.886 (95% CI: 0.869 - 0.901).

The sensitivity of F was 0.167 (95% CI: 0.142 - 0.196) for polyps, 0.263 (95% CI: 0.140 - 0.438) for stage A cancer, and 0.588 (95% CI: 0.539 - 0.635) for stage B/C cancer.

The specificity of IF was 0.991 (95% CI: 0.975 - 0.997).

The sensitivity of IF was 0.037 (95% CI: 0.022 - 0.079) for polyps, 0.481 (95% CI: 0.342 - 0.622) for stage A cancer, and 0.843 (95% CI: 0.763 - 0.898) for stage B/C cancer.

The sensitivity of S was 0.9 for polyps and 0.957 for cancer.

The specificity of a B was 0.978 (95% CI: 0.941 - 0.993).

The sensitivity of a B was 0.887 (95% CI: 0.847 - 0.918) for polyps and 0.917 (95% CI: 0.899 - 0.931) for cancer.

The sensitivity of C was 0.9 (95% CI: 0.875 - 0.921) for polyps and 0.957 (95% CI: 0.843 - 0.993) for cancer.

The rate of major bleeding was 0 with S and B, 0.000085 (95% CI: 0.000027 - 0.00023) with diagnostic C, and 0.00662 (95% CI: 0.005502 - 0.007959) with polypectomy.

The rate of perforation was 0.000143 (95% CI: 0.000007 - 0.000927) with S, 0.000168 (95% CI: 0.000088 - 0.000310) with a B, 0.00197 (95% CI: 0.00168 - 0.002311) with diagnostic C, and 0.00377 (95% CI: 0.003048 - 0.004652) with polypectomy.

Fifty per cent of cancer was derived from polyps, and a polyp took 7 years to transform into CRC.

Of all polyps, S detected 60.6%.

The case-fatality rate was set at 0.818 for perforation due to B and 0.0966 for perforation due to C.

Estimates of effectiveness based on opinion

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
The authors assumed the following:

- 97% of polyps remained benign
- The probability of detecting both benign and malignant polyps in the no screening model was 5 polyps per 1,000 persons per year (which estimates 50% more observed cases of polyps than the incidence of CRC)
- The probability of detecting both types of polyps in the screening models was the same as the sensitivity of screening examinations
- The probability of polyps that could be resected was 50%
- Individuals with resected polyps re-entered the polyp-free and cancer-free health state in the following year
- Undetected cancer remained in Duke's Stage A for 2 years, in Stage B for one year, and in Stage C for one year, at which point its presence became evident clinically if it were still undetected
- The sensitivity of S was the same as that of C within the range of S; and the specificity of S and C were 1.
- In addition, the sensitivity and specificity of each combination for detecting CRC was calculated assuming that the test characteristics of each examination were independent.

Economic analysis

Measure of benefits used in the economic analysis
The summary benefit measure was the number of years of life saved (YOLS). These were obtained from modelling. An annual discount rate of 5% was applied, but the undiscounted results were also reported. The number of perforations was also estimated and reported.

Direct costs
A 5% discount rate was applied as the costs were incurred over a long timeframe. The unit costs were presented, but information on the quantities of resources used was less clear. The health services included in the economic evaluation were F, IF, S, B, C, bowel preparation, biopsy, complication (major bleeding and perforation), pre-hospital work, initial treatment of cancer or polypectomy, outpatient clinic visits, and terminal care. The cost/resource boundary of the payer was adopted. Resource use was mainly estimated from authors' assumptions and some published data. The costs were mainly based on charges, which might not have reflected the true costs, but which represented the costs from the perspective of the payer. The cost of C was derived from experts' opinions, while other costs were estimated from 1989 and 1990 rates. The price year was not reported.

Indirect costs
The indirect costs were not considered.

Currency
Japanese yen (¥). The exchange rate was ¥135 = 1 US dollar ($).

Statistical analysis of costs
The costs were treated deterministically.

Sensitivity analysis
Univariate sensitivity analyses were carried out to assess the robustness of the cost-effectiveness ratios to variations in a number of variables. The variables considered included the sensitivity and specificity of screening, the probability of cancer development from adenomatous polyps, the probability of polyp detection and treatment, and the interval during which polyps transformed to cancer. Also investigated were survival rates after cancer treatment, cost estimates, and discount rates. The ranges used in the analysis were derived from CIs obtained from the literature. The ranges of the cost estimates were not reported. Different ages of initiation and compliance rates were also considered.

Estimated benefits used in the economic analysis
The estimated discounted (undiscounted) YOLS per 100,000 persons screened with strategies 1 to 7 over no screening were:

Strategy 1, ¥92 (405);

Strategy 2, ¥1,073 (4,378);

Strategy 3, ¥1,331 (5,506);

Strategy 4, ¥1,485 (6,088);

Strategy 5, ¥1,592 (6,481);

Strategy 6, ¥1,610 (6,590); and

Strategy 7, ¥2,217 (9,057).

The number of perforations per 100,000 persons screened with each strategy over no screening was 83 with strategy 1, 60 with strategy 2, 307 with strategy 3, 74 with strategy 4, 82 with strategy 5, 105 with strategy 6 and 430 with strategy 7.

Cost results
The estimated total average costs per patient with strategies 1 to 8 were:

Strategy 1, ¥38,670;

Strategy 2, ¥36,090;

Strategy 3, ¥72,660;

Strategy 4, ¥50,740;

Strategy 5, ¥53,170;

Strategy 6, ¥49,850;

Strategy 7, ¥134,390; and

Strategy 8, ¥21,430.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the screening strategies over no screening.

The incremental cost per YOLS with strategies 1 to 7 over no screening was:
Strategy 1, ¥18,683,000 ($138,400);

Strategy 2, ¥1,366,000 ($10,100);

Strategy 3, ¥3,850,000 ($28,500);

Strategy 4, ¥1,974,000 ($14,600);

Strategy 5, ¥2,006,000 ($14,900);

Strategy 6, ¥1,756,000 ($13,100); and
Strategy 7, ¥5,096,000 ($37,700).

F-F-B-C was dominated by IF2y-C, which had the best cost-effectiveness ratio among all strategies. IF-C dominated both IF-B-C and IF-B/S-C. F-C was dominated by the three strategies using annual IF. The incremental cost per YOLS from IF-C to IF/S3y-C was very high (Y13,939,000; $103,000). Therefore, the IF-C strategy was considered the preferred strategy.

The sensitivity analysis showed that, with a younger starting age, more effectiveness would have been obtained but at higher costs. Initiating screening at age 45 had the best cost-effectiveness at Y1,680,000 ($12,400) per YOLS, while the incremental cost of changing the initial screening from 45 to 40 years was greater although still relatively low (Y2,269,000; $16,800). Variations in model assumptions did not produce substantial changes and IF-C remained the preferred option. Discounting made screening less favourable, but the cost-effectiveness of IF-C remained low. The dropout rate had a significant impact on the initiation age. With a 10% dropout rate, screening at age 40 was dominated by screening at age 45. However, when 15 to 20% dropout rates were considered, screening at age 50 dominated earlier initiation ages.

Conclusions, commentary and implications

Author's Conclusions
The strategy of performing immunological faecal occult blood testing (IF) every 2 years, followed by colonoscopy (C) after positive results, was the most cost-effective strategy for screening for colorectal cancer (CRC) in Japan. The analysis also showed that screening should be started at age 45, or even at age 40.

CRD commentary

Selection of comparators:
The rationale for the choice of the comparators was reported and all the relevant combinations of screening strategies were considered in the analysis. The no screening option was also considered, which was appropriate since it may reflect the current approach in some settings. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness:
The analysis of effectiveness used evidence mainly derived from published studies. However, it was unclear whether a systematic review of the literature had been undertaken to identify relevant studies. No information on the primary sources, the sample size and study design was reported. Therefore, the quality of the evidence used in the model was unclear. Similarly, there was limited information on the methods used to combine the primary estimates. Other estimates were derived from authors' assumptions. Most of the key model inputs were varied in the sensitivity analysis to test the robustness of the authors' conclusions.

Validity of estimate of measure of benefit:
The summary benefit measure was appropriate as it captured the impact of the interventions on the patients' health. However, quality of life issues were not considered since the analysis focused on survival. Discounting was carried out, as recommended, and the impact of variations in the discount rates was investigated. Undiscounted results were also reported. The use of YOLS makes comparisons with the benefits of other health care interventions feasible.

Validity of estimate of costs:
The authors explicitly stated the perspective adopted in the study. As such, it appears that all the costs relevant to the payer have been considered in the analysis. Charges were used as proxies for the costs, although the authors acknowledged that true costs would have been more appropriate. However, it was also noted that charges relevant to the payer were used. The unit costs were presented, but the information on resource use was unclear. The source of the cost data was given for all items. The costs were obtained in 1989 and 1990, but the price year was not reported. This makes reflation exercises in other settings difficult. The costs were also presented in US dollars. No

statistical analyses of the costs were carried out, but sensitivity analyses were carried out on key cost estimates.

Other issues:
The authors made some comparisons of their findings with those from other studies and stated that their results were comparable with those reported in the literature. Some differences with other studies were also highlighted. The issue of the generalisability of the study results to other settings was not explicitly addressed, but extensive sensitivity analyses were carried out and these demonstrated the robustness of the base-case results. The authors noted that some data came from studies conducted outside of Japan (particularly from the UK) since local data were not available. This could have introduced some uncertainty into the analysis.

Implications of the study
The study results showed that IF-C at age 45 could be considered the screening option of choice for the detection of CRC in the general population. However, when choosing between the three IF options, the frequency of complications (higher with IF-C) should be considered, particularly when considering the indirect and intangible costs of treating complications.

BERCHI (2004) [118]

Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France

Berchi C, Bouvier V, Reaud J-M, Launoy G. Health Economics 2004;13:227-238.

Health technology
Two approaches for 20 years of biennial colorectal cancer (CRC) screening were studied. The approaches were an automated immunological test (Magstream) and the guaiac stool tests (Haemoccult). Individuals with positive results underwent a colonoscopic investigation.

Disease: Neoplasms; Digestive system diseases.

Type of intervention: Screening.

Hypothesis/study question
The objective of the study was to assess the cost-effectiveness of Magstream versus Haemoccult for 20 years of biennial CRC screening in the general population in France. The authors stated that, despite encouraging results showing the decrease in CRC-related mortality due to screening, no European country had organised widespread mass screening with either the Haemoccult test of Magstream. The perspective of the Social Security Service (the screening organiser) was adopted in the study.

Economic study type: Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of individuals aged 50 to 74 years.

Setting
The setting appears to have been primary care. The economic study was carried out in France.

Dates to which data relate
The effectiveness evidence came from studies published between 1982 and 2001. No dates for resource usage were explicitly reported. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.

Modelling
A Markov model was constructed to determine the costs and benefits of CRC screening in a hypothetical cohort of 165,000 individuals aged 50 to 74 years, who were undergoing biennial CRC screening for 20 years. The model included six health states, which were defined according to the status of the individuals in relation to screening (refusal, positive or negative). The health states were no cancer or adenoma, adenoma less than 1 cm, adenoma more than 1 cm, CRC stage A, B, C (according to Dukes classification) and metastasised, follow-up, and death. The cycle length was one year.

Review/synthesis of previously published studies

Outcomes assessed in the review

- The outcomes estimated from the literature were:
- The prevalence of adenomas in relation to age
- The annual probability of transition of an adenoma of less than 1 cm into one of more than 1 cm
- The annual probability of transition of an adenoma of more than 1 cm into cancer
- The frequency of CRC in screened individuals in relation to age
- The frequency of CRC in patients refusing a test in relation to age
- The occurrence and distribution of CRC per diagnostic stage

- The rate of specific mortality of CRC at 1 to 10 years per diagnostic stage
- The sensitivity and specificity of the two screening tests
- The rate of participation to screening.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature was undertaken. The design of the primary studies was unclear, although the number of participants was given for some studies. Mortality was derived from French life tables, while the occurrence or distribution of CRC was derived from a French registry (screening programme run in Calvados from 1991 to 1994).

Sources searched to identify primary studies: Not stated.

Criteria used to ensure the validity of primary studies: Not stated.

Methods used to judge relevance and validity, and for extracting data: Not stated.

Number of primary studies included:
Eight primary studies provided the evidence.

Method of combination of primary studies
The method used to combine the primary studies was not reported. However, it appears that each estimate has been derived from the most reliable study, while extreme values have been used as ranges in the sensitivity analysis.

Investigation of differences between studies: Not stated.

Results of the review
- The prevalence of adenomas in relation to age was 21 to 53% (range: 26.9 - 58.7).
- The annual probability of the transition of an adenoma of less than 1 cm into one of more than 1 cm was 0.02 (range: 0.01 - 0.04).
- The annual probability of the transition of an adenoma of more than 1 cm into cancer was 0.0085 (range: 0.00425 - 0.017).
- The frequency of CRC in screened individuals in relation to age was 42.1 to 288 per 100,000.
- The frequency of CRC in patients refusing a test in relation to age was 52 to 590 per 100,000.
- The sensitivity of the Haemoccult test was 52% and the specificity was 99.5%.
- The sensitivity of Magstream was 82% (range: 70 - 90) and the specificity was 96% (range: 90 - 100).
- The rate of participation in screening was 43.7%.
- The occurrence and distribution of CRC per diagnostic stage, and the rate of specific mortality of CRC at 1 to 10 years per diagnostic stage, were not reported.

Economic analysis
Measure of benefits used in the economic analysis
The summary benefit measure was the number of life-years saved with each screening strategy. This was obtained using modelling. It would appear that no discounting was applied.

Direct costs
Discounting was relevant since the costs were incurred during a 20-year timeframe. An annual discount rate of 5% was applied. The unit costs were clearly presented, but the information on resource use was limited. The health services included in the economic evaluation were organisation of mass screening campaign, tests (purchasing, distribution, and revelation), colonoscopy, and cancer treatment (dependent on disease stage). A detailed breakdown of the cost items was provided. The costs of diagnosing cancers in individuals with negative tests were also considered. The costs of follow-up consisted of one colonoscopy performed every 3 years, as recommended by French gastroenterologists. The cost/resource boundary of the Social Security Service was adopted. The total costs were estimated using modelling. The costs were estimated mainly using reimbursement rates derived from the Calvados screening campaign. The source of the resource use data was

unclear, although some quantities of services were based on local recommended treatment patterns. The price year was not explicitly reported.

Indirect costs
The indirect costs were not considered.

Currency
Euros (Euro).

Statistical analysis of costs
The costs were treated deterministically.

Sensitivity analysis
Univariate sensitivity analyses were carried out to assess the impact of variations in model inputs on the estimated cost-effectiveness ratios. Variations in the participation rate, costs of tests and colonoscopy, sensitivity and specificity of Magstream, prevalence of disease, and the annual transition rates were explored. In general, the ranges used were derived from the literature.

Estimated benefits used in the economic analysis
The estimated number of life-years saved for a 20-year screening programme was 16.7201 with Magstream and 16.7003 with Haemoccult. The corresponding figures for a 10-year programme were 9.7960 (Magstream) and 9.7901 (Haemoccult), respectively.

Cost results
For a 20-year screening programme, the estimated discounted (undiscounted) cost of screening per targeted person was Euros 238 (Euro 316) with Magstream and Euro 179 (Euro 234) with Haemoccult. The corresponding figures for a 10-year screening programme were Euro 195 (Euro 230) and Euro 151 (Euro 177), respectively.

The greatest cost component was colonoscopic investigation (63% for Magstream and 37% with Haemoccult), followed by screening tests (20% for Magstream and 33% with Haemoccult).

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER) was calculated to combine the costs and benefits of the screening strategies. The incremental cost per life-year saved with Magstream over Haemoccult was Euro 2,980 for a 20-year programme after the costs were discounted, and Euro 7,458 when the costs were not discounted. The corresponding figures for a 10-year programme were Euro 4,141 (discounted) and Euro 8,983 (undiscounted).

The sensitivity analysis showed that the ICER was positively correlated with the participation rate (e.g. a decrease in participation from 43.7 to 20% led to a 50% decrease in the ICER). Similarly, the ICER was positively correlated with the cost of colonoscopy. On the other hand, the ICER was negatively correlated with the cost of cancer treatment. When the cost of the Haemoccult test equalled the cost of Magstream, the ICER was Euro 4,898 for 20 years of screening (18% increase compared with the basic scenario).

For a given specificity, the ICER was negatively correlated with the sensitivity of Magstream, and for a given sensitivity the ICER was negatively correlated with the specificity of Magstream. In particular, with 70% sensitivity, the ICER was Euro 26,107 for 90% specificity and Euro -3,607 with a 100% specificity. Therefore, under particular scenarios, Magstream dominated Haemoccult.

Finally, the cost-effectiveness ratio was very sensitive to the parameters associated with the natural history of CRC.

Conclusions, commentary and implications

Author's conclusions
The substitution of the Haemoccult test with Magstream in mass screening for colorectal cancer (CRC) proved to be a cost-effective strategy from the perspective of the third-party payer in France. However, the results were sensitive to the hypotheses underlying the model used in the analysis.

CRD commentary

Selection of comparators:
The authors provided a justification for the choice of the comparators. Haemoccult (with or without rehydration) represented the most widely used screening strategy, while Magstream was a newer immunological approach. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness:
The analysis of effectiveness used data obtained from completed studies. It was unclear whether a systematic review of the literature was carried out, and limited information on the primary studies was provided. Therefore, it is not possible to assess the validity of the sources used. Some of the evidence came from local registries. The most reliable estimate, among those available in the literature, was selected in the base-case, while estimates from other studies provided the basis for the ranges of values tested in the sensitivity analysis.

Validity of estimate of measure of benefit:
The summary benefit measure was appropriate to determine the impact of the interventions on the patients' health. In addition, it represents a measure widely used in studies evaluating cancer screening programmes and it is comparable with the benefits of other health care interventions. However, the impact of the screening on quality of life, which would have been interesting, was not assessed. No discounting was applied. The use of a discount rate on survival in the sensitivity analysis would have been helpful.

Validity of estimate of costs:
The authors explicitly stated the perspective adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. The unit costs were provided, but the information on resource use was less clear and appears to have been based on local treatment patterns. The price year was not reported, which makes reflation exercises in other settings difficult. The costs were treated deterministically in the base-case, but were then varied in the sensitivity analysis. Discounting was applied but undiscounted results were also reported. The authors noted that charges rather than true costs were used in the analysis, therefore the real costs could have been underestimated.

Other issues:
The authors did not compare their findings with those from other studies. It was stated that most of the data were derived from French sources, which reduces the possibility of transferring the conclusions of the analysis to other settings. However, extensive sensitivity analyses were conducted within reasonable ranges, thus increasing the external validity of the analysis.

Implications of the study
The authors stated that forthcoming results of French population-based experiments with immunological tests would confirm (or not) their hypothesis concerning the quality of immunological testing. If further supporting evidence on Magstream becomes available, French health authorities would have a satisfactorily alternative to guaiac tests.

VAN BALLEGOOIJEN (2003) [116]

A comparison of the cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in the Medicare population.

van Ballegooijen M, Habbema J D F, Boer R, Zauber A G, Brown M L. Agency for Healthcare Research and Quality (AHRQ) 2003 (Technology Assessment): 59.

Publication type: Report

Authors' objectives
Colorectal cancer screening is now recommended in the general population beginning at age 50 for those at average risk. The most common colorectal cancer screening test in use in the United States is the guaiac based fecal occult blood test (FOBT). Colorectal cancer screening is now covered by Medicare with a reimbursement level of $4.50 for the guaiac test. Immunochemical fecal occult blood tests (IFOBT) have tended to be more expensive and have not yet been widely used in the US. In order to inform coverage and payment decisions related to the use of these tests, this report estimates the cost effectiveness of an immunochemical test with test performance parameters that are equivalent to or better than those associated with the guaiac test. We also report the threshold payment level of the immunochemical test relative to the guaiac test, the level of payment for the immunochemical test that would result in cost-effectiveness equivalent to that of the comparative guaiac test.

Type of intervention: Diagnosis

Study design: Modelling, Economic evaluation

Results of the review
The cost-effectiveness of the Haemoccult II FOBT ($1,071 per life year gained) is a very favourable level of cost-effectiveness in comparison to other cancer screening modalities. Immunochemical tests, even with costs per test of $28 per test, still have a cost effectiveness ratio of no more than $4,500 per life year saved. At a payment level of $28 for IFOBT and $4.50 for Haemoccult II, the incremental cost effectiveness ratio (ICER) for IFOBT is $11,000 per additional life-year saved assuming a specificity of 98% for IFOBT and $21,000 per additional life-year saved assuming a specificity of 95% for IFOBT. The threshold payment level of the IFOBT, with 98% specificity for most test parameters considered, was in the range of $7.00 to $13.00, which is only somewhat higher than the $4.50 of the base case Haemoccult II. However when the IFOBT has specificity of 95%, then the threshold values for most test parameters considered were less than zero dollars. Results for IFOBT are much more favourable if Haemoccult SENSA is assumed to be the base case and especially if IFOBT is assumed to operate at the more favourable specificity value of 98%. A threshold payment level of $28 for IFOBT is exceeded if either or both of the following conditions are met: a) IFOBT is assumed to have the lower specificity value of 95% but much better values of sensitivity for the detection of adenomas than Haemoccult SENSA, or b) IFOBT is assumed to have sensitivity values equal to Haemoccult SENSA but the higher specificity value of 98%. If we assume payment rates of $18 and $27 for IFOBT, then the corresponding threshold payment levels are $10 and $17 for Haemoccult II when IFOBT has 98% specificity and $5 and $14 for Haemoccult SENSA when assuming 95% specificity for IFOBT.

Authors' conclusions
Faecal occult blood tests, either guaiac based or immunochemical based, provide for a very cost effective intervention for reducing colorectal cancer incidence and mortality. If the immunochemical focal occult blood test maintains the high specificity of Haemoccult II (98%) and increases sensitivity for colorectal cancer to 70% over that of Haemoccult II (40%), then a unit cost level of approximately $13.00 would provide a comparable cost-effectiveness to Haemoccult II at $4.50 per unit cost. If the specificity of the immunochemical focal occult blood test is assumed to be 95% when the sensitivity for colorectal cancer increases to 70%, then the threshold payment level for IFOBT would actually be lower than the current $4.50. However, further threshold analysis using Haemoccult SENSA as the base case with a sensitivity of 70% for colorectal cancer and specificity of 92.5% indicates that the immunochemical test could achieve a threshold payment level in excess of $28 when the more favourable assumptions about IFOBT are made.

Evidence about the relative specificity and sensitivity of IFOBT in comparison to Haemoccult II and Haemoccult SENSA is sparse and highly uncertain. Therefore the scenarios under which the threshold payment level of $28 is exceeded for IFOBT, although potential possible, cannot be considered to be strongly evidence based. If payment level of $18 and $27 are assumed for IFOBT, corresponding threshold payment levels for Haemoccult II would be higher than current payment levels while this would be true for Haemoccult SENSA only if the lower specificity value of 95% is assumed for IFOBT.

WONG (2004) [120]

Cost-effectiveness analysis of colorectal cancer screening strategies in Singapore: a dynamic decision analytic approach

Wong S S, Leong A P, Leong T-Y Amsterdam, The Netherlands: Amsterdam IOS Press, Medinfo 2004; 104-108

Health technology
Five screening strategies for the detection of colorectal cancer (CRC) in the general population were examined. The strategies were guaiac faecal occult blood test (FOBT), immunochemical FOBT (FOBT-IMM), double contrast barium enema (DCBE), flexible sigmoidoscopy (FSIG), and colonoscopy (COL). FOBT and FOBT-IMM, if negative, were repeated yearly, FSIG every 3 years, DCBE every 5 years, and COL every 10 years. Individuals who tested positive with FOBT, FOBT-IMM, DCBE, and FSIG underwent COL for confirmation.

Type of intervention: Screening.

Hypothesis/study question
The objective of the study was to assess the cost-effectiveness of the five screening strategies for the identification of CRC in Singapore. The authors stressed that each strategy had advantages and disadvantages, but in general the most accurate screening options were also the most expensive. The option of no screening was considered as the basic comparator. The perspective adopted in the study was not reported.

Economic study type: Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of individuals aged 50 to 70 years in the general population.

Setting
The setting was not explicitly reported, but it might have been primary care. The economic study was carried out in Singapore.

Dates to which data relate
Some of the effectiveness evidence was derived from a study published in 1995. No explicit dates for resource use were reported. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and experts' opinions.

Modelling
A semi-Markov model was constructed to simulate the natural history of the disease, and to examine the impact of the five screening strategies on costs and survival in a hypothetical cohort of individuals from the general population. The time horizon of the model was 50 years. The starting age of the patients was 50 years. After a positive result in one of the screening strategies, patients underwent COL. If COL was negative, the patients re-entered screening in 10 years' time. If COL was positive to polyps, the patients entered a polyp follow-up protocol. If COL was positive for cancer, then patients underwent surgery depending on the cancer stage. Examples of possible health states were given in the article and the model was illustrated in detail.

Outcomes assessed in the review
The outcomes estimated from the literature were:
The complication rates, the incidence of cancer and 5-year survival, sensitivity and specificity, and age distribution.

Sources searched to identify primary studies: Not stated.

Criteria used to ensure the validity of primary studies: Not stated.

Methods used to judge relevance, validity, extracting data: Not stated.

Number of primary studies included
The authors explicitly reported the use of two primary studies, but other published sources also appear to have been used.

Method of combination of primary studies: Not stated.

investigation of differences between primary studies: Not stated.

Results of the review

- Complications associated with FSIG and COL:
  - The rate of bleeding was 0.0001 with FSIG and 0.001 with COL;
  - The rate of perforation was 0 with FSIG and 0.0007 with COL; and
  - The rate of death was 0 with FSIG and 0.00005 with COL.
- The incidence of polyps was 0.234.
- The incidence of Dukes A and B was 0.0001385, the incidence of Dukes C and D was 0.0001835, and the incidence of total Dukes A to D was 0.0003220.
- The 5-year survival rate was 0.99 with polyps, 0.8 with Dukes A and B, and 0.2 with Dukes C and D.
- The sensitivity of FOBT was 0.1 for polyps and 0.6 for cancer, while the specificities were 0.9 for polyps and for cancer.
- The sensitivity of FOBT-IMM was 0.4 for polyps and 0.9 for cancer, while the specificities were 0.95 for polyps and for cancer.
- The sensitivity of DCBE was 0.3 for polyps and 0.7 for cancer, while the specificities were 0.9 for polyps and for cancer.
- The sensitivity of FSIF for polyps or cancer was 0.6 and the specificity was 0.98.
- The sensitivity of COL for polyps or cancer was 0.9 and the specificity was 1.
- The age distribution of the participants was 39% in the 50- to 54-year age group, 22% in the 55- to 59-year age group, 22% in the 60- to 64-year age group, and 17% in the 65- to 69-year age group.

Methods used to derive estimates of effectiveness
Some assumptions, based on the expert opinions of local surgeons, were made.

Estimates of effectiveness and key assumptions
Experts' opinions were mixed with data derived from the literature (see Results of the Review). The compliance rate was assumed to be 100%.

Measure of benefits used in the economic analysis
The summary benefit measure was life expectancy. This was obtained from the decision model. Discounting does not appear to have been applied. Life expectancy for ‘no screening’ was computed by setting the value for compliance to zero. The resultant value, 76.32 years, was the life-expectancy of the population without any screening programme.

Direct costs
Discounting does not appear to have been carried out, although it would have been methodologically relevant due to the long timeframe of the model. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were the screening procedures (including histology with FSIG and COL) and other procedures related to complications and treatment (i.e., COL with polypectomy, cancer resection, and the treatment of complications associated with COL). The cost/resource boundary of the study was not reported. Resource use was mainly estimated on the basis of assumptions. The costs were derived from the schedule of charges for a non-subsidised patient in Singapore restructured hospitals. The price year was not reported.

Indirect costs
The indirect costs were not considered in the economic evaluation.

Currency: Singapore dollars (SGD$).

Statistical analysis of costs
The costs were treated deterministically.

Sensitivity analysis
Sensitivity analyses were not carried out.

Estimated benefits used in the economic analysis
The life expectancy by age group and screening strategy was:

- In the age group 50 - 54 years, 25.56 years for FOBT, 25.50 years for FOBT-IMM, 25.79 years for FSIG, 26.03 years for DCBE, and 25.71 years for COL;
- In the age group 55 - 59 years, 21.44 years for FOBT, 21.42 years for FOBT-IMM, 21.74 years for FSIG, 21.95 years for DCBE, and 21.94 years for COL;
- In the age group 60 - 64 years, 17.67 years for FOBT, 17.69 years for FOBT-IMM, 18.02 years for FSIG, 18.19 years for DCBE, and 17.92 years for COL;
- In the age group 65 - 69 years, 14.27 years for FOBT, 14.31 years for FOBT-IMM, 14.56 years for FSIG, 14.73 years for DCBE, and 14.92 years for COL.

Cost results
The estimated costs by age group and screening strategy were:

- In the age group 50 - 54 years, SGD$501.82 with FOBT, SGD$1,050.08 with FOBT-IMM, SGD$1,139.31 with FSIG, SGD$786.34 with DCBE, and SGD$1,252.03 with COL;
- In the age group 55 - 59 years, SGD$382.33 with FOBT, SGD$893.61 with FOBT-IMM, SGD$922.24 with FSIG, SGD$618.75 with DCBE, and SGD$1,218.09 with COL;
- In the age group 60 - 64 years, SGD$252.31 with FOBT, SGD$688.82 with FOBT-IMM, SGD$675.83 with FSIG, SGD$442.56 with DCBE, and SGD$724.56 with COL;
- In the age group 65 - 69 years, SGD$103.08 with FOBT, SGD$340.49 with FOBT-IMM, SGD$365.40 with FSIG, SGD$259.26 with DCBE, and SGD$718.17 with COL.

The cost of no screening was implicitly assumed to be SGD$0.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to compare the costs and benefits of the screening strategies with the no screening option (based on a life expectancy of 76.32 years for patients who received no screening). The methods used to calculate these incremental ratios were described in the article.

The incremental cost per life-year saved by age group and screening strategy was:

- In the age group 50 - 54 years, SGD$288.33 with FOBT, SGD$623.12 with FOBT-IMM, SGD$576.28 with FSIG, SGD$355.07 with DCBE, and SGD$660.35 with COL;
- In the age group 55 - 59 years, SGD$145.70 with FOBT, SGD$342.75 with FOBT-IMM, SGD$315.53 with FSIG, SGD$197.19 with DCBE, and SGD$390.24 with COL;
- In the age group 60 - 64 years, SGD$65.42 with FOBT, SGD$177.69 with FOBT-IMM, SGD$160.81 with FSIG, SGD$101.17 with DCBE, and SGD$176.51 with COL;
- In the age group 65 - 69 years, SGD$18.89 with FOBT, SGD$62.03 with FOBT-IMM, SGD$63.60 with FSIG, SGD$43.86 with DCBE, and SGD$117.72 with COL.

The weighted incremental cost-effectiveness ratio (with respect to no screening) was SGD$162.11 with FOBT, SGD$368.06 with FOBT-IMM, SGD$340.36 with FSIG, SGD$211.57 with DCBE, and SGD$402.24 with COL. The weighted incremental ratios were obtained using the age distribution data for each age group.

Author's conclusions
All the screening strategies improved patient survival, but the faecal occult blood test (FOBT) offered the most acceptable cost-effectiveness ratio.

CRD commentary
Selection of comparators:
The rationale for the choice of the comparators was clear. All interventions represented possible screening options in the authors' setting. The no screening strategy was also considered to be a better representation of the additional costs and life expectancy of the screening interventions. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from experts' opinions and data derived from the literature. However, it was not possible to distinguish which data were derived from the literature and which from experts' assumptions. In addition, it was not stated whether a systematic review of the literature had been undertaken and the primary studies appear to have been identified selectively. The uncertainty around these data was not investigated in a sensitivity analysis. The authors also acknowledged that some model inputs were considered as time invariant, which could have affected the results of the analysis.

Validity of estimate of measure of benefit
The summary benefit measure was appropriate as it reflected the impact of the interventions on patient health. Discounting does not appear to have been applied. Quality of life issues were not investigated. Survival can be compared with the benefits of other health care programmes.

Validity of estimate of costs
The authors did not explicitly state which perspective was adopted in the study. Only the direct costs were included in the analysis. The costs were estimated from hospital charges, which may not have been good proxies for true costs. The unit costs were presented separately from the quantities of resources used, which will allow the study to be replicated in other contexts. The costs were treated deterministically and were specific to the study setting. No discounting was explicitly applied, although it would have been relevant given the long timeframe of the analysis. The price year was not reported, which will hinder reflation exercises in other settings.

Other issues:
The authors stated that their estimation of the cost-effectiveness ratio was considerably lower than that reported in other studies, but this was presumably due, not only to the exclusion of some costs, but also to the approach used to calculate survival. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. Therefore, the external validity of the analysis was low. The study referred to the general population aged 50 to 70 years and this was reflected in the authors' conclusions.

Implications of the study
The authors suggested that further research should identify the key parameters that affect the estimation of both costs and survival.

DANIELS (1995) [114]

Title
Options for screening for colorectal cancer in the Royal Air Force: a cost-effectiveness evaluation Daniels K, McKee M. *Journal of the Royal Army Medical Corps* 1995; 141(3): 142-150

Health technology
The study examined the use of faecal occult blood tests (FOBTs) to detect pre-symptomatic colorectal cancer and its precursor lesions as part of periodic medical examinations and screenings. The options were to start FOBTs at one of the following ages: 30, 35, 40, 45, 50, 55 or 60.

Type of intervention: Screening.

Hypothesis/study question
The objective of the study was to investigate the design of any programme to introduce FOBTs as part of the Royal Air Force's (RAF) existing schedule of periodic medical examinations and screenings, and the age groups to be included, rather than the decision as to whether or not it should be commenced. Although the perspective adopted in the economic analysis was not explicitly reported, it would appear that a third party payer perspective was adopted.

Economic study type: Cost-effectiveness analysis.

Study population
The study population comprised RAF personnel aged 30 or over.

Setting
The study setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
Effectiveness data were derived from studies and reports published between 1998 and 1994. The price year would appear to have been 1992.

Source of effectiveness data
Effectiveness data were derived from a review and synthesis of previously published studies and reports.

Outcomes assessed in the review
The outcomes assessed in the review were: the RAF population by age band and sex, and the 5 yearly average ages of RAF personnel since 1975; the expected age-sex incidence of colorectal cancer in the RAF; the actual incidence and prognosis of colorectal cancer in the RAF; the survival rate by Duke's Stage at diagnosis; the sensitivity of FOBT; the lead time; and the prevalence of positive FOBT results.

Study designs and other criteria for inclusion in the review: Not reported.

Sources Searched to Identify Primary Studies: Not reported.

Criteria used to ensure validity of primary studies: Not reported.

Methods used to judge relevance, validity, extracting data: Not reported.

Number of primary studies included
Data from some 10 published studies and records were used. Data specific to the RAF, such as the determination of the population at risk and the actual incidence of colorectal in the RAF were derived from RAF records.

Method of combination of primary studies
The baseline FOBT sensitivity was derived from three studies. The value determined for this study was estimated from the value that most closely corresponded to two studies and was within the range of a third study.

Investigation of differences between primary studies
The authors did not investigate the differences between the primary studies.

Results of the review
Over a third of the RAF population were below 25 years of age, nearly three quarters under 35 and over four-fifths under 40. The average age of the RAF was within the range 30.5 +/- 0.9 years since 1975.

Age specific rates among the general population were applied to the age-sex distribution of the RAF population. The colorectal cancer rate per 100,000 males (females) ranged between 0.26238 (0.22086) for those aged 15-19, 6.56314 (5.85549) for those aged 35-39, and 127.200 (91.6895) for those aged 60-64.

From January 1969 to June 1994 there were 103 colorectal cancer cases occurring in the RAF population. The average incidence over this period was 4.04 per annum, which was slightly greater than the current incidence predicted from national data of 3.60 per annum.

The 5-year survival rates for those with colorectal cancer at Duke's stage A, B, C or D at diagnosis, were respectively, 80%, 60%, 30%, and 10%.

The baseline FOBT sensitivity for colorectal cancer was estimated to be 55%. FOBT would have an additional sensitivity of two-thirds the initial value for colorectal cancers diagnosed between one and two years later, and one third of this level for colorectal cancers diagnosed between two and three years later.

The baseline prevalence of FOBT results was assumed to be 5%.

Measure of benefits used in the economic analysis
The measure of benefits used in the economic analysis was the number of cases detected. Multiplying the RAF population by the colorectal cancer incidence gave the number of cases detected. This was then multiplied by the sensitivity of FOBT to detect cancers, which was then multiplied by the lead-time effect to obtain the number of cases potentially detected.

Direct costs
Resource use and costs were not reported separately. The direct costs to the RAF, which in this case was the third party payer were included in the analysis. The costs included were: the costs of the FOBT; the personnel costs of testing; the costs of subsequent investigation, which included NHS staff costs assumed to be comparable to those for the RAF; and the costs of colonoscopies. It is unclear if further costs were included in the analysis. FOBT costs were obtained from the manufacturers of the tests. Personnel costs of testing were calculated as the full capitation costs of a senior aircraftman for the time taken to undertake one test, with the information being supplied by RAF laboratories. Additional supply and transport costs were assumed to be negligible, as they would involve existing transport channels. Total costs were reported, which were calculated by multiplying the number in each age group by the cost of the FOBT test, and added to the product of the number of positive FOBT and the cost of a colonoscopy. As all costs were incurred over a short time period, discounting was not relevant and hence was not performed. The price year was not explicitly reported.

Indirect costs: Indirect costs were not included.

Currency: UK pounds sterling (£).

Statistical analysis of costs
Costs were treated as point estimates (i.e., the data were deterministic).

Sensitivity analysis
The authors undertook a sensitivity analysis by varying the costs of a full investigation of FOBT positive cases; using a more expensive FOBT test; an improvement in the specificity of FOBT and thus a reduction in the prevalence of positive FOBTs; and a sensitivity of FOBTs of 90%.

Estimated benefits used in the economic analysis
The estimated benefits of starting FOBTs at one of the following ages were:
30-34 years: 0.253519 cases detected
35-39 years: 0.573216 cases detected
40-44 years: 0.858858 cases detected
45-49 years: 0.852925 cases detected
50-54 years: 0.478361 cases detected
55-59 years: 0.067783 cases detected
60-64 years: 0.006985 cases detected

Cost results
The costs of starting FOBTs at one of the following years were:
30-34 years:,20,905
35-39 years:,14,398
40-44 years:,12,748
45-49 years:,5,592
50-54 years:,16,137
55-59 years:,1400
60-64 years:,89.80.

Synthesis of costs and benefits
Costs and benefits were combined as the cost per case detected. No incremental analysis was performed. The cost per case detected if FOBT was to be started in each of these age bands was:
30-34 years:,82,461
35-39 years:,25,119
40-44 years:,14,843
45-49 years:,6,557
50-54 years:,33,734
55-59 years:,20,667
60-64 years:,12,856.

The authors found that a cost per case detected when starting screening at age 40 was,15,881.

Results of the sensitivity analysis showed that a 66% increase in the cost of an investigation produced a 64% increase in the cost per case detected. Quadrupling the cost of FOBT kits produced only a 3.3% increase in the cost per case detected. An improvement in the specificity of FOBT would reduce the cost per case detected by 68.2%. Setting the sensitivity at 90% would reduce the cost per case detected by 38.9%.

Author's conclusion
The authors did not derive any clear conclusions from their study, reporting only that the study provided information on the costs of various FOBT screening strategies for the RAF, and other Services. However, the authors did point out that the most cost-effective age at which to introduce FOB screening appeared to be age 40.

CRD commentary
Selection of comparators: The authors compared different FOBT strategies, whereby the screening programme was to start in different age groups. However, the authors did not compare FOBT screening with current practice (i.e., five yearly medical examinations) that as the authors reported did not include FOBT testing.

Validity of estimate of measure of effectiveness: The authors did not report that a systematic review was undertaken to identify relevant research and minimise biases. The authors also did not report the methodology of the review of the literature, nor the sources used to identify research. When more than one study was used to derive a measure of effectiveness, the authors combined effectiveness estimates using narrative methods, rather than adopting pooling methods. The authors did not investigate the differences between the primary studies. All studies however, appeared to be relevant to the setting of the present study, as they all had a UK setting. The authors also undertook a sensitivity analysis to estimate the effect of varying sensitivity and specificity rates of the FOBT test.

Given the level of reporting on the methods of the review it is difficult to assess whether the best available evidence has been used.

Validity of estimate of measure of benefit: The estimate of measure of benefit was obtained by multiplying the RAF population by the colorectal cancer incidence. This was then multiplied by the sensitivity of FOBT to detect cancers, which was then multiplied by the lead-time effect to obtain the number of cases potentially detected. All of these estimates were derived from the literature or from RAF records.

Validity of estimate of costs: All categories of cost relevant to the perspective adopted appear to have been included in the analysis, and it would appear that no relevant costs were omitted. The authors reported that any additional supply and transport costs were assumed to be negligible as they involved existing transport channels. Resource use quantities and unit costs were not reported separately, which will limit the generalisability of the authors' results. Costs were derived from the authors' setting and from NHS reviews. Appropriate sensitivity analyses of costs were performed, with the ranges used appearing to be appropriate. As all costs were incurred over a short time period, discounting was not relevant, and appropriately was not performed. The price year was not explicitly reported but appears to have been 1992. Having to assume the price year in which costs were based will make the results of any inflationary exercise look dubious.

Other issues: The authors did not compare their findings with those from other studies. The issue of generalisability to other settings was partly addressed through the sensitivity analysis. The authors do not appear to have presented their results selectively. However they did not report any clear conclusions from their study. The main limitation of this study was that an incremental cost-effectiveness analysis was not undertaken to determine the most cost-effective FOBT strategy. Hence, it might not be the case that starting FOBT in the age band 45-49 years or at age 40 is the most cost-effective strategy (as reported by the authors as it had the lowest average cost per case detected). It is possible that incremental analysis may have shown that starting FOBT at a different age band would have a lower incremental cost-effectiveness ratio (i.e., an extra case detected could be achieved at a lower cost) or at a cost which society or the decision maker was willing to stand. The authors also reported limitations to their study, namely that decisions on which screening programme to undertake would ideally be derived from a randomised controlled trial, rather than from extrapolations from published data.

Implications of the study
The authors reported that the aim of the study was not to seek to argue for or against the introduction of a Service-wide screening programme, but to indicate the consequences of various possible options.

Other publications of related interest
Hardcastle J. Randomized control trial of faecal occult blood screening for colorectal cancer: results for the first 144,103 patients. Eur J Cancer Prev 1991;1(Suppl 2): 21.

Thomas W M, Pye G, Hardcastle J, et al. Faecal occult blood screening for colorectal neoplasia: a randomised trial of three days or six days of tests. Br J Surg 1990; 77 (3):277-9.

Source of funding: None stated