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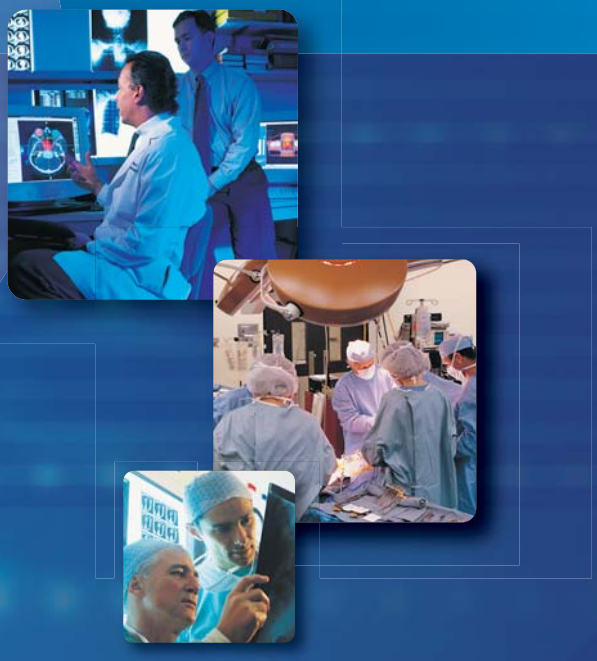
Fecal Immunochemical Tests for Colorectal Cancer Screening: A Systematic Review of Accuracy and Compliance



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Fecal Immunochemical Tests for Colorectal Cancer Screening: A Systematic Review of Accuracy and Compliance

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September 2009

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure that they were addressed appropriately.

Reviewers

These individuals kindly provided comments on this report:

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Industry: BTNX Inc. was given an opportunity to comment on an earlier version of this report.

ACRONYMS AND ABBREVIATIONS

AAP	advanced adenomatous polyps
CI	confidence interval
CRC	colorectal cancer
CS	colonoscopy
ELISA	enzyme-linked immunosorbent assay
FIT	fecal immunochemical test
FOBT	fecal occult blood test
FS	flexible sigmoidoscopy
gFOBT	guaiac fecal occult blood test
HTA	health technology assessment
HTIS	Health Technology Inquiry Service
mg	milligram
mL	millilitre
mm	millimetre
ng	nanogram
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
RCT	randomized controlled trial
RR	relative risk
RPHA	reverse passive hemagglutination
SD	standard deviation
USPSTF	US Preventive Services Task Force

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TITLE: Fecal Immunochemical Tests for Colorectal Cancer Screening: A Systematic Review of Accuracy and Compliance

DATE: September 2009

EXECUTIVE SUMMARY

Context and Policy Issues

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths among men and women in Canada. Compared to no screening, screening for CRC is associated with a reduction in incidence and mortality. Early detection results in an improved prognosis for individuals with CRC. At least two types of stool-based screening tests are used in Canada to detect occult blood from bleeding cancers and adenomas. These include the guaiac fecal occult blood test (gFOBT) and the fecal immunochemical test (FIT). The purpose of this report is to review the evidence regarding the diagnostic accuracy and patient compliance in screening with FIT.

Research Questions

1. What is the accuracy (sensitivity and specificity) of fecal immunochemical tests compared to guaiac tests for colorectal cancer screening?
2. What is the evidence that compliance is higher with the fecal immunochemical test compared to the guaiac test for colorectal cancer screening?

Methods

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches were run in PubMed and The Cochrane Library. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and Canadian guidelines. The search was restricted to English language clinical articles published between 2004 and April 2009. Regular alerts were established on EMBASE and MEDLINE, and information that was retrieved via alerts was current to June 15, 2009.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of key papers. Two independent reviewers screened articles for selection.

Summary of Findings

The literature search identified one health technology assessment (HTA), two systematic reviews, two randomized controlled trials (RCTs) that were not included in the two systematic reviews, and six observational studies that reported on the diagnostic accuracy of FIT compared with gFOBT. In addition, one RCT and one observational study were identified that evaluated patient compliance.

A 2007 HTA by the New Zealand Health Technology Assessment program examined the clinical and cost-effectiveness of screening tests for colorectal cancer. Six observational studies and one RCT evaluating FIT were included, and six types of FIT were evaluated. In most studies, FITs did not perform as well as gFOBTs in diagnostic accuracy. In a single study, one FIT, HemeSelect, performed equally as well as or better than the two gFOBTs (Hemoccult II and Hemoccult SENSA). The authors of the HTA concluded that the evidence regarding the clinical effectiveness of FIT compared with gFOBT is weak, mainly because of the paucity of high quality studies.

The Norwegian Knowledge Centre for Health Services conducted a systematic review of methods for CRC screening. The authors identified two systematic reviews and one

guideline regarding the diagnostic accuracy of FIT. The sensitivities of FIT ranged from 82% to 94% across the three reports, and the specificity was reported to be 87% across the three reports. The authors did not make any conclusions about the accuracy of FIT compared with gFOBT. Another systematic review published in 2008 by Whitlock et al. included nine cohort studies evaluating FITs, including HemeSelect and FlexSure. The authors concluded that FITs that had better sensitivities and similar specificities as Hemoccult II may represent reasonable CRC screening test alternatives. Results from the systematic review by Whitlock et al. were used to help inform a 2008 US Preventive Services Task Force (USPSTF) recommendation on colorectal cancer screening.

Two RCTs comparing the diagnostic accuracy of FIT to gFOBT are included in the current report. A 2009 RCT found that the FIT (OC-Sensor Micro) detected more advanced neoplasia at a hemoglobin cut-off level of 50 nanograms (ng)/millilitre (mL) and 200 ng/mL than did the gFOBT (Hemoccult II). The detection rates for CRC were similar at all cut-off levels. A 2008 RCT compared the performance of FIT with that of gFOBT and reported that, while the specificity of gFOBT to detect CRC or advanced adenomas was statistically significantly higher than FIT, the detection rates of FIT were statistically significantly higher than those of gFOBT. A third RCT compared patient participation rates between FIT and gFOBT, and found a higher rate of compliance with FIT (35.8%) compared with gFOBT (30.4%).

Four observational studies that were included reached similar conclusions regarding the comparison of FIT and gFOBT tests. Overall, they found that FIT was more sensitive for the detection of cancers and significant adenomas than gFOBT, and had a higher specificity than gFOBT for detecting advanced adenomas.

Another study evaluated the use of a two-tier screening approach that involved the use of the relatively inexpensive gFOBT test as a first-round screening tool, and only followed up with FIT in those individuals with a positive gFOBT. The authors concluded that this approach was effective in identifying those with cancer or clinically significant adenomas.

A comparison of the bedside FIT (Prevent ID CC) to gFOBT (Hemoccult) and to the human hemoglobin enzyme-linked immunosorbent assay (ELISA [Immundiagnostik AG]) was made in a 2006 study. The authors concluded that the beside FIT was an accurate test with similar performance characteristics to the ELISA, and that the sensitivity of the bedside FIT was statistically significantly greater than that of the gFOBT.

A 2005 study in a community-based rural setting found that FIT (InForm) had a higher patient participation rate than gFOBT (Hemoccult II).

Conclusions and Implications for Decision-Making or Policy-Making

The results of this review suggest that FIT may be effective as a method of screening for CRC and advanced adenomas, and that FIT may be more effective when compared to other screening tests, such as gFOBT. In particular, the HemeSelect, FlexSure OBT, and OC-Sensor Micro FITs have demonstrated improved diagnostic performance characteristics compared with the gFOBT. All included studies that compared participation rates of FIT with other screening tests demonstrated that FIT had higher completion rates than the other tests, including gFOBT. The type of FIT and associated costs, the appropriate hemoglobin cut-off to use, and the capacity for follow-up by colonoscopy or flexible sigmoidoscopy may contribute to deciding if FIT is an appropriate CRC screening tool.

1 CONTEXT AND POLICY ISSUES

In 2009, in Canada, it is estimated that more than 22,000 new cases of colorectal cancer (CRC) will be diagnosed, and that there will be more than 9,000 deaths due to CRC.[1] CRC is the second leading cause of cancer-related deaths among men and women in Canada.[1] Screening for CRC is associated with a reduction in incidence and mortality.[2] If detected at an early stage, the prognosis for an individual with CRC improves.[1] Several Canadian jurisdictions have an active screening program or are in the process of developing one.[3] In addition, the Canadian Partnership Against Cancer has developed a national Colorectal Cancer Screening Network with the aim of improving screening programs across Canada.[4]

At least two types of stool-based CRC screening tests are used in Canada:[3] the guaiac fecal occult blood test (gFOBT) and the fecal immunochemical test (FIT). Both tests detect occult blood from intestinal bleeding.[5] The guaiac-based test reacts with the peroxidase activity of the heme subunit of the hemoglobin.[6] A disadvantage of this test is that it can also react to dietary peroxidases, such as those found in some plant products and in red meat.[6] The immunochemical-based test reacts to the globin subunit of hemoglobin and is specific for human hemoglobin. Therefore, the participant does not need to follow any dietary restrictions before completing the test.[6] The amount of occult blood that is detected is believed to be associated with the degree of pathology.[5] Newer FITs are able to quantify the amount of hemoglobin in the provided stool sample. This provides the advantage of selecting a hemoglobin level cut-off that is associated with a known sensitivity and specificity.[5]

Poor participant compliance with stool-based tests is a barrier to CRC screening.[7] This report will review the literature regarding the diagnostic accuracy of FIT, as well as information pertaining to the compliance of screening with FIT.

2 RESEARCH QUESTIONS

1. What is the accuracy (sensitivity and specificity) of fecal immunochemical tests compared to guaiac tests for colorectal cancer screening?
2. What is the evidence that compliance is higher with the fecal immunochemical test compared to the guaiac test for colorectal cancer screening?

3 METHODS

3.1 Literature Search

Peer-reviewed literature searches were conducted to obtain published literature for this review. All search strategies were developed by an information specialist, with input from the project team.

The following bibliographic databases were searched through the Ovid interface: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, and EMBASE. Parallel searches were run in PubMed and The Cochrane Library. The search strategy was comprised of both controlled vocabulary, such as the US National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Methodological filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and Canadian guidelines. The detailed search strategies appear in Appendix 1.

The search was restricted to English language clinical articles that were published between 2004 and April 2009. Regular alerts were established on EMBASE and MEDLINE, and information retrieved via alerts was current to June 15, 2009.

Grey literature (literature that is not commercially published) was identified by searching the websites of health technology assessment and related agencies, professional

associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by hand searching the bibliographies and abstracts of key papers.

3.2 Article Selection

Two reviewers (MM and KC) independently screened titles and abstracts that were retrieved by the literature search. The same two reviewers independently evaluated the full-text publications during final article selection. Primary studies (RCTs, controlled clinical trials, or observational studies) that compared FIT with a gFOBT were considered for inclusion. Secondary studies (health technology assessments [HTA, a multidisciplinary study including a clinical systematic review], systematic reviews, or systematic review-based meta-analyses) were included if they reported findings based on direct or indirect comparisons. The outcomes of interest included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to detect advanced adenomas and CRC. Studies that compared participation rates between the two tests were also considered for inclusion. Studies were excluded if they were not of an eligible study design (HTA, systematic review, meta-analysis, randomized controlled trial, controlled clinical trial, or an observational study comparing the two types of FOBTs), if the intervention was not a FIT, or if the comparator was not a gFOBT. Studies that reported CRC mortality rates in the absence of data on sensitivity and specificity were excluded. Secondary studies were excluded if the reported methodology did not appear to be robust (i.e., did not include a search of more than one database or did not involve multiple reviewers in the literature selection process). Any differences between the two reviewers in the selection of articles for inclusion were resolved by consensus. Studies that met inclusion criteria and were reviewed in a systematic review that was included in this report were not appraised separately.

4 SUMMARY OF FINDINGS

The search of electronic databases identified a total of 352 publications. A search of the grey literature and hand searching of selected bibliographies identified an additional 33 publications. After screening of titles and abstracts, 302 citations were excluded, and 83 were retrieved for full-text screening. Thirteen publications were included in this report, and the remaining 70 articles were excluded. A flow chart[8] documenting the process of study selection is provided in Appendix 2.

The literature search identified one HTA,[9] two systematic reviews,[2,10] two additional RCTs[11,12] that were not included in the systematic reviews, and six observational studies[13-18]on the diagnostic accuracy of FIT compared with gFOBT. One RCT[19] and one observational study[20] evaluated compliance with each test. Pertinent study details are discussed in the next section of this report. Tables containing relevant descriptive information regarding the summarized RCTs (Table 1) and observational studies (Table 2) can be found in Appendix 3. No evidence-based Canadian guidelines were identified.

4.1 Health Technology Assessments

In 2007, the New Zealand Health Technology Assessment (NZHTA) program published a HTA examining the clinical and cost-effectiveness of screening tests for colorectal cancer.[9] The report was prepared for the New Zealand Ministry of Health's National Screening Unit to assist in decision-making regarding an organized screening program for CRC in New Zealand. A systematic literature search was conducted from 1997 to November 2004, and identified 1,986 citations. The reviewers sought studies that assessed the clinical and cost-effectiveness of FOBT compared with no screening, FIT compared with gFOBT, flexible sigmoidoscopy (FS) compared with no screening, and FS in combination with FOBT screening compared

with individual screening methods. For clinical effectiveness, only RCTs were included, except the assessment of the diagnostic accuracy of FIT compared with gFOBT, for which all study types were included. The clinical outcomes of interest included diagnostic performance (sensitivity, specificity, PPV, and NPV) and screening-related outcomes, including compliance with test procedures and test completion rates. Studies were excluded if the methods were not systematic, the studies were in a non-English language, or they were non-human studies. The HTA included 56 articles. For the current report, only data on FITs are discussed.

From the search, six primary studies — five observational studies (three cross-sectional studies, one retrospective cohort study, and one non-randomized study) assessing the diagnostic performance of FIT, and one RCT comparing participation rates of FIT and gFOBT —were included in the HTA. Pertinent details of the included studies are provided in Table 1. No pooling of the data from individual studies was performed by the authors of the HTA. Five secondary studies were identified. It was not possible to determine the study types of these five reports (i.e., systematic reviews or meta-analyses) from the details provided in the HTA report, and the authors of this report did not review these studies separately; however, three of the studies seemed to follow systematic review methods. The types of FIT tests that were evaluated were FlexSure OBT, HemeSelect/HemeSp, OC-Hemodia, and InSure.

Table 1: Characteristics of Primary Studies Included in the HTA Produced by the New Zealand HTA Program[9]

Author, Year, and Study Type	Sample Size	Mean Age ± SD (Years)	Male (%)	Symptomatic (%) or Average Risk (%)	Types of FIT and gFOBT Evaluated
Rozen et al. (2007), cross-sectional study	403 participants	60.2 ± 10.8	46	Symptomatic: 3 Average risk: 21	**FIT:** • FlexSure OBT • HemeSelect **gFOBT:** • Hemoccult II • HemoccultSENSA
Cole et al. (2003), RCT	4,000 eligible participants	Range 50 to 69	NR	NR	**FIT:** • InSure • FlexSure OBT **gFOBT:** • HemoccultSENSA
Ko et al. (2003), non-randomized study	5,929 participants	65.4 ± 10.5	98	NR	**FIT:** • FlexSure OBT **gFOBT:** • HemoccultSENSA
Cheng et al. (2002), cross-sectional study	7,411 participants	46.8 ± 9.9	44.8	Stated that population was asymptomatic	**FIT:** • OC-Hemodia **gFOBT:** • CFOBB
Zappa et al. (2001), cohort (un-specified, seems to be retrospective)	41,774 participants	range 50 to 70	59.7	NR	**FIT:** • Immudia-HemSp (also known as HemeSelect) **gFOBT:** • Hemoccult II
Rozen et al. (2000), cross-sectional study	1,410 participants	60.9 ± 11.0	47	Symptomatic: 3 Average risk: 21	**FIT:** • FlexSure OBT **gFOBT:** • HemoccultSENSA

FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; HTA = health technology assessment; NR = not reported; SD = standard deviation

Overall, the authors reported that there was limited evidence available from the included observational studies that compared FIT to gFOBT. In the studies that compare the two types of tests directly, the FIT HemeSelect (also known as HemSp) had more favourable performance test characteristics than the gFOBTs to which it was compared. For instance, in a single study by Rozen et al. (2007), the HemeSelect was compared with the Hemoccult II and HemoccultSENSA gFOBTs. The sensitivity of HemeSelect to detect any neoplasm was 35% (95% Confidence Interval [CI], 16% to 57%); specificity: 99% (95% CI, 97% to 100%); PPV: 67% (95% CI, 35% to 90%); and NPV: 96% (95% CI, 93% to 98%). In the same study, the sensitivity, specificity, and PPV of HemeSelect were also superior to another FIT (FlexSure OBT) for the detection of any colorectal neoplasia. Authors of the HTA noted that Rozen et al. had received some industry support and that the study population (403 participants; 54% female) was predominately asymptomatic (97%) and had been repeatedly screened. These limitations suggested that the findings may not be generalizable to all populations who are eligible for screening. The one RCT that was included in the New Zealand HTA report included 4,000 eligible participants aged 50 years to 69 years who were randomly chosen from electoral districts, and compared the participation rates of those using two FITs (InSure and FlexSure OBT) and one gFOBT (HemoccultSENSA) at 12 weeks. The participation rate of those using InSure was statistically significantly higher than the rates of participation of those using the other two tests (InSure 39.6%; FlexSure OBT 30.5%; HemoccultSENSA 23.4%; $P < 0.01$ for all combinations).

The authors stated that there was limited evidence available from head-to-head studies comparing FIT to gFOBT, and that there were no RCTs evaluating diagnostic performance. They stated that there were flaws in the design and quality of the included studies that may have introduced bias and limited the conclusions. These limitations included possible verification bias in studies where only those with a positive FIT or gFOBT result received follow-up by CS. In addition, bias may have been introduced from studies that received industry support, studies that did not conduct FIT and gFOBT testing simultaneously, and studies that had low participation rates. The authors concluded that, given the paucity of RCTs or other high- quality studies on FITs, the evidence regarding their clinical effectiveness is weak compared with gFOBT. It was also noted that if further published evidence becomes available, the topic should be re-visited.

4.2 Systematic Reviews and Meta-analyses

The Norwegian Knowledge Centre for the Health Services conducted a systematic review of CRC screening methods for the Norwegian Directorate for Health.[10] Hviding et al.[10] performed a systematic literature search to identify relevant secondary studies, including HTAs, systematic reviews, meta-analyses, and guidelines. Primary studies were not searched systematically, and instead, hand searching through reference lists and website searches were performed to identify potentially relevant primary studies. One-hundred and fifty-four citations were retrieved by the literature search, and an additional 80 citations were identified by manual searching. It was unclear if these 80 studies were exclusively primary studies. To be considered for inclusion, studies had to have included participants 50 years of age or older; have used gFBOT, FIT, FS, or colonoscopy (CS) as a primary screening method and made comparisons to either no screening or another screening method; have reported on outcomes, including diagnostic performance, harms, and compliance; and have been published in English or a Scandinavian language. Studies were excluded if they included participants at a high risk of developing CRC or if the intervention was genetic testing. Forty-five articles met the inclusion criteria. Only studies reporting on the effectiveness of FIT will be discussed in this report.

The authors identified one cluster randomized trial comparing FIT to no screening. No diagnostic performance measures were reported.

The participation rate was evaluated. The trial, which included more than 190,000 participants with a median age range of 40 years to 49 years, took place in China. The participants who were randomized to be in the screening group received the FIT (a reverse passive hemagglutination [RPHA] test) and answered a health questionnaire. Participants with a positive FIT result or with a health questionnaire score over a pre-determined value were offered follow-up using FS. Those with a negative FS result were asked to complete a second FIT. If the second FIT result was positive, they were offered a CS as follow-up for confirmation. If possible, all lesions were removed at the time of diagnosis. Details about further treatment and follow-up were not reported. The participation rate was reported to be 66.4%, but it is unclear if this rate includes those who used the follow-up screening that was offered to them. Authors reported a statistically significant reduction in rectal cancer mortality in the FIT group compared to the no-screening group. Some participants did not receive follow-up, regardless of whether or not the FIT result was positive or negative. Therefore, the authors were unable to calculate sensitivity or specificity. This is a limitation of the report.

The authors of the systematic review[10] identified two additional systematic reviews (Kerr et al. [2007] and Whitlock et al. [2007][2]) and one guideline (Levin et al. [2008]) on the diagnostic accuracy of FIT. The number and description of studies that were evaluated in the three reports were not described. Hviding et al.[10] did not pool diagnostic test performance characteristics from individual studies. The authors reported that the sensitivities of FIT ranged from 82% to 94% across the three reports, and that the specificity was 87% across all studies for patients who received a follow-up using CS or FS. It was unclear how these values were derived or if all patients, regardless of test result, received follow-up. If only those patients with a positive FIT result received follow-up, the value of the reported sensitivities and specificities is limited. Hviding et al.[10] identified one RCT by Segnan et al. (2007) that compared the attendance and detection rates for FIT, CS, and FS. The RCT included more than 18,000 participants. Hviding et al. provided no further methodological and study details. The attendance rates were 32.3% for FIT, 32.3% for FS, and 26.5% for CS. It was not reported if these rates were significantly different based on a statistical comparison. Segnan et al. calculated the number needed to screen to detect one carcinoma, which was 264 for FIT, 60 for FS, and 53 for CS. The authors of the systematic review did not make any conclusions about the accuracy of FIT compared with gFOBT.

In 2008, Whitlock et al.[2] published a systematic review designed to address areas that were identified as knowledge gaps in a previous 2002 US Preventive Services Task Force (USPSTF) recommendation. The systematic review was used to help inform a 2008 USPSTF recommendation on colorectal cancer screening.[21] The literature search identified a total of 3,948 citations. To be considered for inclusion, studies had to involve participants 40 years of age or more who were of average risk for CRC, and who were recruited from a primary-care or comparable setting. Study types included were systematic reviews, RCTs, diagnostic cohort studies, screening registries, and select case series. The quality of eligible studies was assessed using criteria established by the USPSTF,[22] and one of three grades of evidence was assigned: good, fair, or poor. The grades of evidence were defined as: "In general, a good study meets all criteria for that study design; a fair study does not meet all criteria but is judged to have no fatal flaw that invalidates its results; and a poor study contains a fatal flaw."[22] In the current report, only data on accuracy of FIT compared with gFOBT are presented. The outcomes of interest included sensitivity and specificity. Nine fair or good quality cohort studies evaluating the use of FITs among average-risk participants were identified. It was not stated where all the studies took place. Two of the nine studies compared at least one FIT with a gFOBT. The FITs that were evaluated included HemeSelect (this test is marketed as MagStream HemSp) and FlexSure. The remaining seven studies evaluated the performance of FIT compared with the gold standard (CS [for a positive FIT result] or FS [for a negative FIT result]), exclusively. The

sensitivity of FITs across the nine studies ranged from 61% to 91%, and the specificity ranged from 91% to 98%. For gFOBT (Hemoccult II), the authors reported a sensitivity range of 25% to 38%, calculated from one of the two comparative studies that were included in their review and another systematic review. The specificity of Hemoccult II was reported in one comparative study, and ranged from 98% to 99%. When categorized according to the size of polyp or adenoma, the sensitivity of FIT for advanced neoplasia or large adenoma ranged from 27% to 67%, compared with 16% to 31% for gFOBT. The authors reported that there was limited evidence that the test performance of FITs in studies that used a two- or three- day sample collection instead of one day may be improved. In addition, studies may have used different cut-off levels for positivity. These factors may have contributed to the range in sensitivities and specificities that were reported. Authors concluded that FITs with greater sensitivities than and similar specificities as Hemoccult II may be reasonable CRC screening test alternatives. Two of nine studies compared FIT with gFOBT. The remaining studies evaluated the performance of FIT alone. For a screening strategy that includes FOB testing, USPSTF recommends the annual use of a test with a sensitivity of 70% or more and with a specificity of more than 90%.[21] The USPSTF suggests that the tests that meet these parameters include HemoccultSENSA and FITs that are similar to MagStream HemSp.[21]

4.3 Randomized Controlled Trials

A 2009 RCT comparing FIT to gFOBT was conducted by Hol et al.[11] The trial was performed in the Netherlands, and randomized 10,011 average-risk and screening-naïve participants aged 50 to 74 years (approximately 47% male). A computer-generated model was used so that households were randomized to receive a FIT or a gFOBT after stratification for age, sex, and socio-economic status. There were no diet or medication restrictions. Participants with inflammatory bowel disease, CRC, or other major health problems, or who had a CS, FS, or barium contrast enema in the last three years, were excluded. The gFOBT that was used was Hemoccult II. Participants were required to sample from three consecutive bowel movements. The test cards were not re-hydrated for analysis. For quality control, 10% of the test cards were evaluated by a second technician who was blinded to the first result. Discrepancies were resolved by a third technician. The FIT that was used was OC-Sensor Micro, which required one fecal sample from one bowel movement. The test cards were analyzed using the automatic OC-Sensor Micro instrument. A positive test result was considered to be a hemoglobin level of 50 nanograms (ng)/millilitre (mL) or more. The follow-up for a positive FIT or gFOBT result was CS, which was performed by experienced personnel. Given that only those who had a positive test result received follow-up, sensitivity or specificity was not measured in this study. The positivity rate for FIT was calculated at hemoglobin levels ranging from 50 ng/mL to 200 ng/mL, at 50 ng increments. The detection rate was defined as the proportion of participants having advanced neoplasia. Advanced neoplasia included cases of CRC or adenomas 10 millimetres (mm) or greater, or with histology showing 25% or more villous component or high-grade dysplasia. Among participants, 2.8% (95% CI; 2.2% to 3.6%) had a positive gFOBT result. Positive FIT results ranged from 8.1% (95% CI; 7.2% to 9.1%) at a 50 ng/mL cut-off to 3.5% (95% CI; 2.9% to 4.2%) at a 200 ng/mL cut-off. A statistically significant decrease in positive test results was observed between hemoglobin level cut-offs of 50 ng/mL and 75 ng/mL (8.1% and 5.7%, respectively; $P < 0.05$). With the use of FIT, more advanced neoplasia was detected at the lowest cut-off level that was evaluated, 50 ng/mL (3.2%; 95% CI; 2.6% to 3.9%) and at the highest that was evaluated, 200 ng/mL (2.1%; 95% CI; 1.6% to 2.6%) compared with gFOBT (1.2%; 95% CI; 0.8% to 1.7%). At a cut-off of 50 ng/mL to 100 ng/mL, the detection rate of using FIT for advanced neoplasia was more than two times greater than that of using gFOBT ($P < 0.05$). The detection rates of using FIT and gFOBT for CRC were not statistically significantly different. The number of CS that was needed to be performed to find at least one

advanced neoplasia (number needed to scope) favoured the use of FIT compared with gFOBT at all cut-off levels. A goal of the study was to determine the optimal hemoglobin level cut-off to use with FIT that was associated with a low false-positive rate, yet did not compromise the detection rate and number needed to scope. The authors concluded that a value of 75 ng/mL was optimal. It was noted that this value could be modified, based on a country's capacity for follow-up. The use of an increased cut-off value would result in a lower detection rate, but this may be considered if there is less capacity to screen using FS or CS. The authors reported that there were no conflicts of interest. This study showed that the use of FIT was more effective at detecting advanced neoplasia compared with gFOBT.

A randomized trial by van Rossum et al. published in 2008[12] compared the performance of FIT with gFOBT. The trial took place in Amsterdam, where 20,623 screening-naïve participants aged 50 years to 75 years (48.3% male) were randomized to receive gFOBT (Hemoccult II) or FIT (OC-Sensor Micro). There were no diet restrictions, and it was not stated whether or not there were any medication restrictions. A hemoglobin cut-off level of 100 ng/mL was used to designate a positive FIT result. The follow-up for a positive FIT or gFOBT result was CS, performed by experienced personnel. The test completion rate was statistically significantly greater for FIT (59.6%) compared with gFOBT (46.9%; $P < 0.01$). Among participants, 456 tested positive with FIT (2.4%) and gFOBT (5.5%; $P < 0.01$), and CS was performed among 383 participants. Specificity was calculated using the rare disease assumption. The authors stated that this approach can overestimate the true specificities, especially in the case of more common lesions and tests with greater sensitivity. The specificity of gFOBT (99.0% [95% CI; 98.9% to 99.3%]) to detect CRC or advanced adenomas was statistically significantly higher compared with that of FIT (97.8% [95% CI; 97.4% to 98.1%]) ($P < 0.01$). The detection rates of FIT for advanced adenomas and CRC (from the intention-to-screen population) were statistically significantly higher compared with those of gFOBT ($P < 0.01$). There was no statistically significant difference in the PPV between the two tests for the detection of CRC or advanced adenomas. There was also no statistically significant difference between the two tests in the number needed to scope to find one CRC. Taking these findings and the differences in participation rates between tests into consideration, the authors concluded that the use of gFOBT underestimates the prevalence of advanced adenomas and CRC compared with FIT. Given that the specificity of FIT was lower compared with gFOBT, more individuals would be referred for negative CS in the FIT group. This study highlights the need for appropriate capacity for follow-up when using the FIT. The authors did not report if there were any conflicts of interest.

A cluster-randomized trial was performed by Federici et al. (2005)[23] to compare the participation rates between FIT and gFOBT. The study took place in Italy. The practices of 130 general practitioners (GPs) were recruited and were randomized. Practices were assigned either a gFOBT (Hemo-Fec) or FIT (OC-Hemodia). Among the 7,320 participants of 50 years to 75 years of age, 3,604 individuals received a gFOBT (Hemo-Fec), and 3,716 received the FIT OC-Hemodia. No additional information about the risk profile of the participants was given. The FIT group had a higher rate of compliance (35.8%) compared with 30.4% for gFOBT (Relative Risk [RR] 1.20 [95% CI; 1.02 to 1.44]). Although the FIT rate was higher, the participation rates were low. The authors reported that 1,194 general practitioners were invited to participate, and 292 expressed an interest (24.5% participation rate), with 130 being randomly selected from this group. This relatively low participation rate also highlights the opportunity for increased engagement in the screening process at the level of general practitioner.

4.4 Observational Studies

Guittet et al. (2009)[13] compared the diagnostic performance of a FIT (Immudia/RPHA) with the gFOBT, Hemoccult II. Both tests were completed by 20,322 average-risk participants.

The age range was 50 years to 74 years, and 50.8% of those with follow-up results were male. The study took place in France. (A previous publication[24] reported on a subset of the study samples, and will not be discussed separately in the current report.) The participants were instructed to use two fecal samples from two different days for FIT, and two fecal samples each from three consecutive stools for the gFOBT. Participants were not required to use the same stools for both tests. No dietary restrictions were imposed, and it was not stated if there were any medication restrictions. Those analyzing gFOBT results were blinded to FIT results. The FIT results were analyzed using the MagStream 1000 automated device. The hemoglobin level cut-off that was used for FIT was 20 ng/mL. Advanced colonic neoplasia was defined as high-risk adenomas (adenomas measuring 10 mm or more or adenomas with high-grade dysplasia) or invasive cancer. All 1,615 participants who had a positive result from one or both tests were offered a follow-up with CS, and 1,387 (85.8%) participated. The authors did not calculate sensitivity or specificity, because negative results did not go for further evaluation using CS. They calculated a ratio of sensitivity (the number of true positives for FIT divided by the number of true positives for gFOBT) where a ratio of more than 1 is interpreted as the sensitivity of FIT being greater compared with gFOBT. Of the participants undergoing CS, 30.5% had a positive gFOBT result, and 80.5% had a positive FIT result. The PPV of FIT was statistically significantly lower for invasive cancer (4.0%) compared with that of gFOBT (6.9%*;* P = 0.03), and higher for high-risk adenomas (23.4% versus 19.5%; P value not stated). The sensitivity ratios for invasive cancer (1.48 [95% CI; 1.16 to 1.89]) and high-risk adenomas (3.32 [95% CI; 2.70 to 4.97]) favoured FIT compared with gFOBT, with the increase in sensitivity being statistically significant for invasive cancers (P < 0.001). The authors reported that most of the cancers that were detected using FIT were of good prognosis. The authors stated that the use of FIT was more sensitive for rectal cancers compared to sites in the colon. The authors concluded that the gain in sensitivity with FIT for high-risk adenomas was independent of the location of the lesion. The authors did not report if there were any conflicts of interest. A limitation of this study is that a direct calculation of sensitivity and specificity was not possible, given that individuals with a negative test result did not receive follow-up. More individuals had a positive FIT result, which could have an impact on CS resources.

A recent study by Rozen et al. (2009)[14] compared the effectiveness of FIT and gFOBT to detect neoplasms. A second objective was to determine the FIT threshold that would provide equal or better sensitivity compared to gFOBT. The study took place in Israel, and recruited 330 participants who were scheduled for CS. A proportion of the participants had a previous positive gFOBT result (138/330; 41.8%), were above-average risk for CRC (73%), required follow-up screening (4%), or were mildly symptomatic (23%). The remaining participants (192/330; 58.2%) had tested negative in a previous gFOBT and included some who had volunteered to participate. The proportion of participants with a previous negative gFOBT was not reported. The mean age was 64.5± 9.8 years (standard deviation [SD]), and 54.8% were male. The gFOBT that was evaluated was Hemoccult SENSA, and OC-Sensor Micro was the FIT that was assessed. Participants were instructed to take fecal samples from three consecutive bowel movements. No diet restrictions were imposed, and patients were requested to refrain from taking acetylsalicylic acid and other anti-coagulants for one week before CS. For FIT, three tests were performed. Test cards were processed using the OC-Sensor Micro automated analyzer, and were expressed in ng hemoglobin/mL. Results from the first test and the highest result that was obtained for each of the second and third tests were evaluated over a range of hemoglobin threshold levels from 50 ng to 200 ng in 25 ng increments. It was not stated if those conducting analyses were blind to other test results. Follow-up using CS detected CRC in six participants, and advanced adenomatous polyps (AAP) were detected in 26 participants. Diagnostic performance measures were presented for CRC and AAP combined. AAP was defined as polyps 10 mm or more in diameter, or having 20% or more villous histology, or any amount of high-grade

dysplasia. The sensitivity and specificity of gFOBT were 53.1% (95% CI; 35.8% to 70.4%) and 59.4% (95% CI; 53.8% to 65.0%), respectively. The number needed to scope to detect one neoplasm was 8.1. At a 50 mg per mL cut-off, FIT had a similar sensitivity and a higher specificity of 94.0% (95% CI; 91.3% to 96.7%). The number of CS needed to be performed to detect one neoplasm was 2.1. When the higher result of two FIT tests was calculated for the same cut-off level, the sensitivity and specificity were 68.8% (95% CI; 52.7% to 84.8%) and 91.9% (95% CI; 88.9% to 95.0%), respectively. The estimated number needed to scope to detect one neoplasm remained at 2.1. The performance of three tests increased the sensitivity by 9.1% and increased the number needed to scope to 2.6. Appendix 3, Table 2 summarizes the findings on diagnostic accuracy. Based on the findings, the authors concluded that in the study population, the use of FIT had a higher specificity compared with gFOBT for significant neoplasms and resulted in a decreased number of colonoscopies that had to be performed to detect one neoplasm. The number of FITs to be conducted for each participant can be modified to reflect the capacity of a screening program. The authors concluded that performing more than one FIT for the same individual can improve diagnostic performance. A strength of this study is that all patients, regardless of test results, received follow-up by the gold-standard reference CS, thereby allowing calculation of sensitivity and specificity. However, this study included a proportion (approximately 41%) that were either high risk, symptomatic, or had a previous gFOBT. The remaining proportion either had a previous negative gFOBT or had volunteered to participate. These sample characteristics might not be reflective of a general screening population, and represent a limitation of this study.

A 2007 study by Allison et al.[15] assessed the diagnostic performance of the gFOBT (Hemoccult SENSA), the FIT (FlexSure OBT), and the combination of the two tests. A total of 5,841 average-risk participants were included in the study. Approximately 47.5% of the study population was male. The mean age was not stated (the participants were more than 50 years of age). The follow-up consisted of CS for positive results and FS for negative results. The study took place in the US. Stool samples were taken from three consecutive bowel movements (one for each test). Each test was provided on separate cards, and the combination card included both tests. With the combination card, the FIT was developed if the gFOBT result was positive. Authors proposed that this saved on costs that were associated with developing FITs, even in instances of a negative gFOBT result. Patients were asked to avoid vitamin C for three days before and during the collection period. No other dietary or medication restrictions were stated. Those analyzing tests were blinded to the results of the other test. The sensitivity and specificity for advanced neoplasia in the left colon (rectum, sigmoid colon, or descending colon) within two years after screening was evaluated. Table 2 in Appendix 3 provides a detailed summary of the relevant findings pertaining to diagnostic accuracy. Based on study findings, the authors concluded that the sensitivity and specificity of using FIT for distal cancers and the specificity of FIT for advanced adenomas were greater compared with gFOBT. A strength of this study is that participants with negative test results underwent follow-up using FS. The follow-up using FS meant that study authors could evaluate the detection of neoplasia in the left colon. If a right-sided neoplasia was detected using CS in an individual with a positive test result, the authors considered this to be a false-positive. The authors stated that there were such cases, and this would have resulted in underestimation in test sensitivity.

Fraser et al. (2007)[16] used a two-tiered approach to evaluate the use of FIT in a gFOBT-positive population. The rationale was to use the relatively inexpensive gFOBT as a first-round screening tool, and to use FIT only in individuals with a positive gFOBT result. The objective was to decrease the number of follow-up CSs required. The study took place in the UK. During the first phase of testing, of the 1,124 individuals who had a positive gFOBT (hema-screen) result, 558 (49.6%) agreed to participate in further screening. Data from phase 2 screening using FIT (hema-screen DEVEL-A-

TAB and SPECIFIC systems) and from follow-up using CS were available for 556 participants. The FIT result was positive in 254 individuals, of whom 47 (18.5%) had cancer, and 54 (21.3%) had high-risk polyps. Among those with a FIT negative result and a positive gFOBT result (302 participants), 14 (4.7%) had cancer or high-risk polyps. The sensitivity and specificity of this approach for the detection of cancer and high-risk polyps were 87.8% (95% CI; 80.1% to 92.9%) and 65.3% (95% CI; 60.6% to 69.7%), respectively. The PPV and NPV were 2.53 (2.19 to 2.93) and 0.19 (0.11 to 0.31), respectively. The authors concluded that the two-tiered approach was effective in identifying those with cancer or clinically significant adenomas. The study authors noted that this strategy was to be used by the Scottish Bowel Screening Programme, in which all individuals in the target screening age range will be sent a gFOBT. If the gFOBT result is "strongly positive" (at least five of six spots positive on the gFOBT kit card), then the individual will be referred for CS immediately. Those with a "weak positive" (one to four [of six] spots positive on the gFOBT kit card) will be asked to complete a FIT. This strategy may be useful in jurisdictions where resources for follow-up using CS or FS are limited.

A study by Hoepffner et al. (2006)[17] was conducted to compare the performance of the bedside FIT (Prevent ID CC) to the gFOBT (Hemoccult) and to the human hemoglobin enzyme-linked immunosorbent assay (ELISA; [Immunodiagnostik AG]). The study, which was conducted in Germany, included 387 participants. The median age was 51 years, and 48.3% of participants were male. Follow-up was done using CS. Of the participants, 237 had inflammatory bowel disease or symptoms of colonic disease. The remaining participants who were scheduled for routine screening were otherwise healthy. No dietary or medication restrictions were imposed on participants. Stool samples were provided by participants, and the test cards were prepared by laboratory staff. Table 2 in Appendix 3 provides a detailed summary of the relevant findings pertaining to diagnostic accuracy. Based on the findings, the authors concluded that the bedside FIT was an accurate test with similar performance characteristics to the established method of ELISA, and that the sensitivity of the bedside FIT was statistically significantly greater than that of the gFOBT ($P < 0.05$). The authors declared no conflicts of interest. A limitation of this study is that most of the participants were at elevated risk or were symptomatic. This sample population is not representative of a typical screening population. The value of this study's results in informing the development of a screening program may be limited.

A paired comparison study of the FIT (InSure) and the gFOBT (Hemoccult II SENSA) was conducted by Smith et al. (2006).[18] The Australian-based study involved a screening cohort of 2,351 participants. The average age of participants was 64 years, and 47.8% of the study population was male. Participants were excluded if they had known benign colonic disorders associated with bleeding or if they had previously undergone colorectal surgery. The study also involved a diagnostic cohort (n = 161) of symptomatic individuals that were referred for colonoscopy. The average age in the diagnostic cohort was 66.2 years, and 46.5% were male. All participants from both cohorts provided stool samples from two consecutive bowel movements for FIT, and from three consecutive bowel movements for gFOBT. It was not clear from the article if those analyzing the tests were blinded to results. The follow-up for those in the diagnostic cohort and for those with a positive test result was CS. The individual performing the CS was not always blinded to the test results, but was not aware of which test (gFOBT or FIT) was positive. Table 2 in Appendix 3 provides a detailed summary of the relevant findings pertaining to diagnostic accuracy. Overall, 4.7% of the tests were positive by gFOBT, and 6.7% by FIT. The PPVs for all cancers and significant adenomas (greater than 10 mm) did not differ statistically between the two tests (26.0% for FIT and 20.2% for gFOBT). The combined positivity rate of FIT for the screening and diagnostic cohorts to detect cancer (all stages) was 87.5%, compared to 54.2% for gFOBT (a paired difference of 33.0% [95% CI; 11.2% to 55.4%]). The positivity rate for the detection of significant adenomas, villous

changes, high-grade dysplasia, serrated histology, or three of more adenomas of any size or histopathology was 42.6% for FIT, and 23.0% for gFOBT (a paired difference of 19.7% [95% CI; 7.0% to 32.4%]). The authors concluded that FIT was more sensitive for cancers and significant adenomas than gFOBT. The authors declared that there were no conflicts of interest. A limitation of this study is that individuals with a negative test result did not receive follow-up. Therefore, the study authors were unable to calculate sensitivity and specificity. In addition, the study included a diagnostic cohort of symptomatic individuals; this sample population is not representative of a typical screening population. The use of results from this study to inform the development of a screening program may be limited.

Hughes et al. (2005)[20] compared the participation rates between a gFOBT (Hemoccult II) and a FIT (InForm [also known as InSure outside of Australia]) in a rural community setting in Australia. The 3,358 participants received one of the two test kits (72.0% received the FIT, and 28.0% received the gFOBT). More than 75% of the participants were between the ages of 50 years and 69 years, and 48.5% were male. The overall participation rate was 36.3%. Those with a positive test result for either test were instructed to make an appointment with their family doctor to discuss follow-up options, which included CS. The participation rate for those offered CS was 94.8%. Participation rate was higher with the FIT than with the gFOBT (odds ratio [OR] = 1.9, 95% CI; 1.6 to 2.2). The authors concluded that the FIT had a higher participation rate than gFOBT in a community-based rural setting, likely due to its user-friendly characteristics (including less handling of stool samples). Funding was received by the manufacturers of the FIT to subsidize the costs of the kits.

4.5 Limitations

This review has several limitations. A limited literature search was conducted, and studies that were not cited in the databases searched may have been omitted. In addition, articles published from 2004 to the present and in the English language were eligible for inclusion. Potentially relevant evidence that was published before 2004 would have been excluded. The HTA[9] that was summarized in this report included papers that were published from 1997 to 2004. Five of the six primary studies that were included in the HTA were published before 2004. Despite the inclusion of this HTA, date restriction is a limitation of this report. The eligibility of identified studies for inclusion in this report was assessed exclusively using methodological details in the published article, and additional information was not sought from study authors. In addition, studies that had been previously reviewed as part of an included HTA or systematic review were not appraised separately for this report.

Most of the articles meeting inclusion criteria for this review were observational studies. Observational studies lack a control group and may be subject to bias. The inclusion of observational studies was limited to those that made a direct comparison between gFOBT and FIT. Two RCTs evaluating the diagnostic performance of FITs compared with gFOBTs were identified in the literature search. Most of the studies that were appraised in the included systematic reviews evaluated FIT alone, and made indirect comparisons with studies involving gFOBT. None of the included systematic reviews conducted a meta-analysis. Instead, they reported diagnostic performance from individual studies. Some of the FITs that were evaluated in this report may be unavailable in Canada. The FITs that are licensed for sale in Canada can be found by searching Health Canada's Medical Devices Active License Listing.[25] In addition, the FITs that were appraised often used different hemoglobin cut-off levels, which were not always stated in the article. Differences in cut-off levels would likely have an impact on the test sensitivity. While most of the studies reported single-test performance characteristics, several studies asked that participants complete the FIT or gFOBT in duplicate or triplicate. Multiple tests may increase accuracy, although such an approach would add costs and would likely be unfeasible for a population-based screening program.

A limitation of many of the included studies was that follow-up was typically only performed in cases of positive test results. Given that those with negative test results did not receive follow-up, it was not possible in all studies to calculate sensitivity and specificity. Follow-up for a positive test was typically done using CS. The use of CS is associated with complications.[12] Therefore, study investigators may choose not to subject all participants to follow-up. In addition, the use of FS, which is considered to be less invasive, is associated with decreased detection of adenomas in the right side of the colon.[12] In cases where follow-up was performed, the clinical experience of the provider was not always described.

Several studies evaluated a patient population that was at elevated risk, because patients had a pre-existing colonic condition, were symptomatic, or had a previous positive FOBT. Results from such studies may be of limited value when considering the evidence for the development of a screening program in a screening-naïve population. Most of the studies were performed outside Canada, and some of the tests that were used may be unavailable in Canada.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION-MAKING OR POLICY-MAKING

Overall, the studies that assessed the diagnostic performance of FIT showed that it was comparable to gFOBT for the detection of cancer and clinically significant advanced adenomas. The included HTA[9] reported that two tests, HemeSelect and FlexSure OBT, performed as well as or better than the most commonly appraised gFOBT, Hemoccult (including Hemoccult II). The HTA and the systematic reviews noted that more high-quality studies, including RCTs with gFOBT as a comparator, are needed. Our report included two RCTs that were published after the search time frame of the HTA and systematic reviews.[11,12] Both RCTs evaluated the OC-Sensor Micro (FIT) and the Hemoccult II (gFOBT). Both trials reported that the detection rate of using FIT for advanced adenomas was higher than that of gFOBT. One RCT reported a statistically significant increase in the detection rate of CRC using FIT.[12] Several studies compared the participation rates using FIT to other screening tests. All studies reported that the completion rates were higher when using FIT compared with the other tests, including gFOBT. The authors of these studies attributed the increase in compliance to a decreased handling of stool required with FITs.

A relatively wide range of sensitivities and specificities were noted for both FITs and gFOBTs. Many of the studies included in the current report evaluated different types of tests, thereby adding to the challenge of comparing studies and their findings. In addition to the type of test, variations in diagnostic performance may also be attributed to the population being screened (average risk versus elevated risk), the intensity of bleeding from the lesions detected, the presence of colonic conditions associated with increased bleeding, the pre-test instructions (diet and medication restrictions), the reference test used for follow-up, and variations in test processing procedures.

The capacity for follow-up of positive tests using CS or FS is likely to be an issue in some Canadian jurisdictions. Several studies proposed approaches to modify the amount of follow-up that is needed. These included a two-tiered approach in which individuals with a positive gFOBT result subsequently completed a FIT. Individuals received follow-up using CS only if the FIT result was also positive. This approach reduced the number of CSs required. Several studies investigated hemoglobin cut-off levels for a positive FIT result. In this case, jurisdictions could modify the cut-off that is used in accordance with the capacity for follow-up using CS or FS.

The results of this review suggest that FIT may be effective as a screening method for CRC, and may be more effective when compared to other screening tests such as gFOBT. In particular, the FITs, HemeSelect, FlexSure OBT, and OC-

Sensor Micro have improved diagnostic performance characteristics compared with the gFOBTs that were used as comparators. The evidence for the effectiveness of OC-Sensor Micro comes from two RCTs. RCTs present high-quality evidence. To more accurately assess the impact of screening, more evidence is needed from additional high-quality studies, including RCTs that evaluate the sensitivity and specificity of these tests. The limitations of the included studies should be considered during decision-making. Other considerations, such as the type of FIT, the costs that are associated with FIT (including the test cards and the quantitative analyzer, if appropriate), the appropriate hemoglobin cut-off level to use, and the capacity for follow-up using CS or FS, may contribute to the decision about whether or not FIT is an appropriate CRC screening tool.

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APPENDIX 1: SEARCH STRATEGIES

OVERVIEW	
Interface:	Ovid
Databases:	EMBASE <1996 to present> Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 - Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	April 22, 2009
Alerts:	Monthly search updates began April 27, 2009 and ran until June 15, 2009.
Study Types:	Health technology assessments; systematic reviews; meta-analyses; randomized controlled trials; controlled clinical trials; observational studies and guidelines.
Limits:	Publication years 2004-April 2009 English language
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
Exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
* or $	At the end of a word indicates truncation.
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.jw.	Journal word
.md.	Methodology
.mp.	Mapping alias (searches title, abstract, heading words, table of contents and key phrase identifiers)

Ovid MEDLINE Strategy		
Line #	**Search Strategy**	**Results**
Fecal Immunochemical Tests:		
1	Feces/ or (Faecal or fecal or feces or faeces).ti,ab.	87274
2	Occult blood/ or (occult or FIT or FITs or FOB or FOBs or iFOB or iFOBs or OBT or OBTs or FOBT or FOBTs or iFOBT or iFOBTs or I-FOBT or I-FOBTs or immunochemical or immunologic* or immunoassay or immuno chemical or immunohistochemical).ti,ab.	352174
3	1 and 2	4630
Colorectal Cancer:		
4	exp Colorectal neoplasms/ or Colorectal tumor/ or Rectal cancer/	111884
5	((colorectal or colon or rectal or rectum or sigmoid or anal or anus or perianal or circumanal) and (cancer* or neoplas* or tumo?r* or carcinoma* or biopsy or biopsies)).ti,ab.	119764
6	CRC.ti,ab.	4946
7	4 or 5 or 6	154232
8	(HemeSelect or FOBGold or FOB Gold or SENTiFOB or OC Auto Micro 80).ti,ab.	29
9	(3 and 7) or 8	1995
10	9	1995
11	limit 10 to english language	1752
12	limit 11 to yr="2004 -Current"	691
SR/HTA/MA Filter:		
13	Meta-analysis.pt.	21898
14	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/	38045
15	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	24496
16	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	3454
17	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	5499
18	(data synthes* or data extraction* or data abstraction*).ti,ab.	8014
19	(handsearch* or hand search*).ti,ab.	3142
20	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	8295
21	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	1431
22	(meta regression* or metaregression* or mega regression*).ti,ab.	861
23	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	53692
24	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	43496
25	(cochrane or health technology assessment or evidence report).jw.	6873
26	(meta-analysis or systematic review).md.	0

Ovid MEDLINE Strategy		
Line #	**Search Strategy**	**Results**
27	or/13-26	106418
RCT Filter:		
28	Randomized Controlled Trial.pt.	275695
29	Randomized Controlled Trials as Topic/	61680
30	Randomized Controlled Trial/	275695
31	Randomization/	65056
32	Random Allocation/	65056
33	Double-Blind Method/	102557
34	Double Blind Procedure/	0
35	Double-Blind Studies/	102557
36	Single-Blind Method/	13090
37	Single Blind Procedure/	0
38	Single-Blind Studies/	13090
39	Placebos/	28175
40	Placebo/	0
41	(random* or sham or placebo*).ti,ab,hw.	701443
42	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	141168
43	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	233
44	or/28-43	720485
CCT Filter: (With Built-In Human Filter)		
45	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	350900
46	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	461815
47	Multicenter Study.pt.	110597
48	Randomized Controlled Trial/	275695
49	Randomized Controlled Trials as Topic/	61680
50	Controlled Clinical Trial/	79903
51	Controlled Clinical Trials as Topic/	4008
52	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/	455220
53	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/	150949
54	Multicenter Study/ or Multicenter Study as Topic/	110597
55	Randomization/	65056
56	Random Allocation/	65056
57	Double-Blind Method/	102557
58	Double Blind Procedure/	0
59	Double-Blind Studies/	102557
60	Single-Blind Method/	13090
61	Single Blind Procedure/	0
62	Single-Blind Studies/	13090

Ovid MEDLINE Strategy		
Line #	**Search Strategy**	**Results**
63	Placebos/	28175
64	Placebo/	0
65	Control Groups/	1203
66	Control Group/	1203
67	Cross-Over Studies/ or Crossover Procedure/	24385
68	(random* or sham or placebo*).ti,ab,hw.	701443
69	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	141168
70	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	233
71	(control* adj3 (study or studies or trial*)).ti,ab,hw.	604847
72	(clinical adj3 (study or studies or trial*)).ti,ab,hw.	740410
73	(Nonrandom* or non random* or non-random* or quasi-random*).ti,ab,hw.	19380
74	(phase adj3 (study or studies or trial*)).ti,ab,hw.	63123
75	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.	37390
76	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.	135483
77	(allocated adj1 to).ti,ab,hw.	16653
78	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	11722
79	trial.ti.	83887
80	or/45-79	1377877
81	exp animals/	14272399
82	exp animal experimentation/	4214
83	exp models animal/	309925
84	exp animal experiment/	4214
85	nonhuman/	0
86	exp vertebrate/	13835164
87	animal.po.	0
88	or/81-87	14279720
89	exp humans/	10855209
90	exp human experiment/	0
91	human.po.	0
92	or/89-91	10855209
93	88 not 92	3424511
94	80 not 93	1242544
Observational Studies:		
95	exp cohort studies/	721936
96	cohort$.tw.	146222
97	controlled clinical trial.pt.	79903
98	epidemiologic methods/	24321
99	limit 98 to yr=1966-1989	11411
100	exp case-control studies/	431562

Ovid MEDLINE Strategy		
Line #	**Search Strategy**	**Results**
101	(case$ and control$).tw.	229913
102	(case$ and series).tw.	85772
103	Case reports.pt.	1431398
104	(case$ adj2 report$).tw.	287401
105	(case$ adj2 stud$).tw.	97233
106	or/95-97,99-105	2799437
107	exp cohort analysis/	721936
108	exp longitudinal study/	655591
109	exp prospective study/	263099
110	exp follow-up/	0
111	exp case control study/	431562
112	exp case study/	1431398
113	Case report/	1431398
114	or/107-113	2425051
115	106 or 114	2799437
Guideline Filter:		
116	Guidelines as topic/ or Health Planning Guidelines/ or Practice Guidelines as Topic/ or Consensus Development Conferences as Topic/ or Critical Pathways/	80370
117	(Guideline or Practice Guideline or Consensus Development Conference or Consensus Development Conference, NIH).pt.	24545
118	((critical adj (path? or pathway? or protocol?)) or (care adj (map? or path? or plan? or pathway? or consensus))).ti,ab.	6110
119	(guideline* or standards).ti.	49053
120	(expert consensus or consensus statement or consensus conference* or consensus development or clinical guideline* or practice guideline* or practice parameter* or position statement* or policy statement* or CPG or CPGs or treatment protocol* or best practice*).ti,ab.	45673
121	or/116-120	163803
122	12 and (27 or 44 or 94 or 115 or 121)	374

Ovid EMBASE Strategy		
Line #	**Search Strategy**	**Results**
Fecal Immunochemical Tests:		
1	Feces/ or (Faecal or fecal or feces or faeces).ti,ab.	24821
2	Occult blood/ or (occult or FIT or FITs or FOB or FOBs or iFOB or iFOBs or OBT or OBTs or FOBT or FOBTs or iFOBT or iFOBTs or I-FOBT or I-FOBTs or immunochemical or immunologic* or immunoassay or immuno chemical or immunohistochemical).ti,ab.	166082
3	1 and 2	2095
4	exp Colorectal neoplasms/ or Colorectal tumor/ or Rectal cancer/	10501
5	((colorectal or colon or rectal or rectum or sigmoid or anal or anus or perianal or circumanal) and (cancer* or neoplas* or tumo?r* or carcinoma* or biopsy or biopsies)).ti,ab.	70572
6	CRC.ti,ab.	3960
7	4 or 5 or 6	73517
8	(HemeSelect or FOBGold or FOB Gold or SENTiFOB or OC Auto Micro 80).ti,ab.	16
9	(3 and 7) or 8	1151
10	9	1151
11	limit 10 to english language	1017
12	limit 11 to yr="2004 -Current"	529
SR/HTA/MA Filter:		
13	meta-analysis.pt.	0
14	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/	99939
15	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.	19174
16	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.	1977
17	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.	3559
18	(data synthes* or data extraction* or data abstraction*).ti,ab.	6494
19	(handsearch* or hand search*).ti,ab.	1657
20	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.	3504
21	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.	1058
22	(meta regression* or metaregression* or mega regression*).ti,ab.	659
23	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	64515
24	(medline or Cochrane or pubmed or medlars).ti,ab,hw.	35489
25	(cochrane or health technology assessment or evidence report).jw.	2852
26	(meta-analysis or systematic review).md.	0

Ovid EMBASE Strategy		
Line #	**Search Strategy**	**Results**
27	or/13-26	144914
RCT Filter:		
28	Randomized Controlled Trial.pt.	0
29	Randomized Controlled Trials as Topic/	140752
30	Randomized Controlled Trial/	140752
31	Randomization/	24924
32	Random Allocation/	24924
33	Double-Blind Method/	53809
34	Double Blind Procedure/	53809
35	Double-Blind Studies/	53809
36	Single-Blind Method/	7328
37	Single Blind Procedure/	7328
38	Single-Blind Studies/	7328
39	Placebos/	89649
40	Placebo/	89649
41	(random* or sham or placebo*).ti,ab,hw.	413331
42	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	73795
43	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	128
44	or/28-43	418729
CCT Filter: (With Built-In Human Filter)		
45	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	0
46	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	0
47	Multicenter Study.pt.	0
48	Randomized Controlled Trial/	140752
49	Randomized Controlled Trials as Topic/	140752
50	Controlled Clinical Trial/	62769
51	Controlled Clinical Trials as Topic/	62769
52	Clinical Trial/ or Phase 2 Clinical Trial/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/	452271
53	Clinical Trials as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/	452271
54	Multicenter Study/ or Multicenter Study as Topic/	41224
55	Randomization/	24924
56	Random Allocation/	24924
57	Double-Blind Method/	53809
58	Double Blind Procedure/	53809
59	Double-Blind Studies/	53809
60	Single-Blind Method/	7328
61	Single Blind Procedure/	7328
62	Single-Blind Studies/	7328

Ovid EMBASE Strategy		
Line #	**Search Strategy**	**Results**
63	Placebos/	89649
64	Placebo/	89649
65	Control Groups/	3933
66	Control Group/	3933
67	Cross-Over Studies/ or Crossover Procedure/	17440
68	(random* or sham or placebo*).ti,ab,hw.	413331
69	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	73795
70	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	128
71	(control* adj3 (study or studies or trial*)).ti,ab,hw.	2395457
72	(clinical adj3 (study or studies or trial*)).ti,ab,hw.	1221570
73	(Nonrandom* or non random* or non-random* or quasi-random*).ti,ab,hw.	11440
74	(phase adj3 (study or studies or trial*)).ti,ab,hw.	44065
75	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw.	12925
76	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw.	56280
77	(allocated adj1 to).ti,ab,hw.	9441
78	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	10234
79	trial.ti.	48173
80	or/45-79	3033310
81	exp animals/	3307
82	exp animal experimentation/	630229
83	exp models animal/	377965
84	exp animal experiment/	630229
85	nonhuman/	1864629
86	exp vertebrate/	49199
87	animal.po.	0
88	or/81-87	1897990
89	exp humans/	4112560
90	exp human experiment/	216927
91	Human.po.	0
92	or/89-91	4162687
93	88 not 92	1400631
94	80 not 93	2158201
Observational Filter:		
95	exp cohort studies/	216929
96	Cohort$.tw.	108232
97	controlled clinical trial.pt.	0
98	epidemiologic methods/	4009
99	limit 98 to yr=1966-1989	0

Ovid EMBASE Strategy		
Line #	**Search Strategy**	**Results**
100	exp case-control studies/	2349950
101	(case$ and control$).tw.	134785
102	(case$ and series).tw.	48320
103	case reports.pt.	0
104	(case$ adj2 report$).tw.	153299
105	(case$ adj2 stud$).tw.	59076
106	or/95-97,99-105	2722382
107	exp cohort analysis/	216929
108	exp longitudinal study/	29692
109	exp prospective study/	86708
110	exp follow-up/	295306
111	exp case control study/	2349950
112	exp case study/	16028
113	case report/	555329
114	or/107-113	3146845
115	106 or 114	3248148
CPG Filter:		
116	*practice guideline/ or *clinical pathway/ or *clinical protocol/ or *consensus development/ or *good clinical practice/	10596
117	(guideline* or standards).ti.	25068
118	(critical adj (path? or pathway? or protocol?)).ti,ab.	633
119	(practice parameter$ or position statement$).ti,ab.	1200
120	guideline?.ti.	20424
121	(expert consensus or consensus statement or consensus conference* or consensus development or clinical guideline* or practice guideline* or policy statement* or CPG or CPGs or treatment protocol* or best practice*).ti,ab.	29862
122	(care adj (map? or path? or plan? or pathway? or consensus)).ti,ab.	2171
123	or/116-122	58097
124	12 and (27 or 44 or 94 or 115 or 123)	442

OTHER DATABASES	
PubMed	Search conducted for in process records using keywords and the same limits and study types as per the Medline search, with syntax adjusted for the PubMed database.
Cochrane Library Issue 2, 2009	Same MeSH, keywords, and date limits used as per Medline search, excluding study type restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Dates for Search:	May 22, 2009 – May 24, 2009
Keywords:	Included terms for Fecal Immunochemical Tests for colorectal cancer screening.
Limits:	Publication years 2004 –present

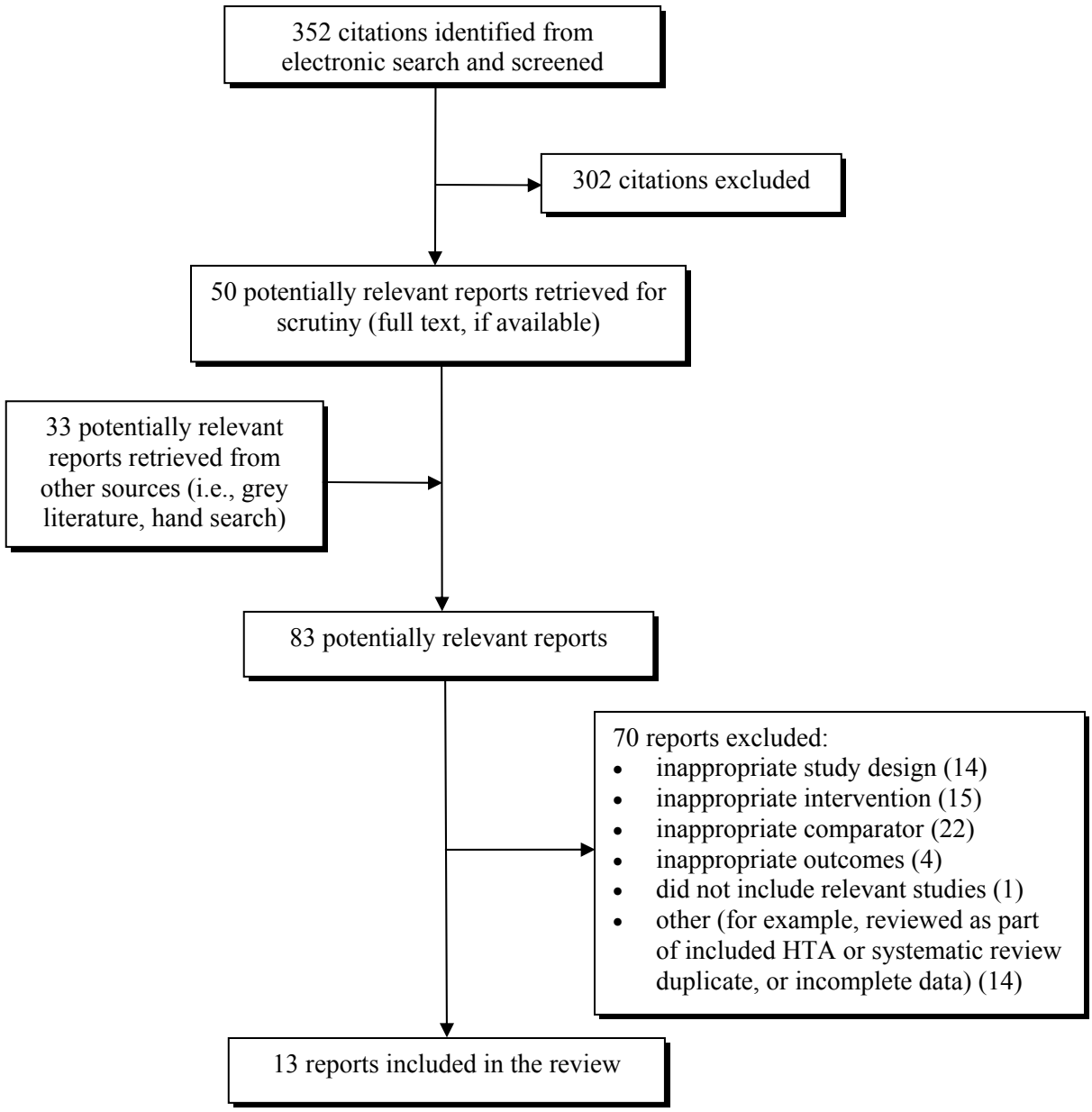
The following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/index.php/en/cadth/products), were searched:

- Health Technology Assessment Agencies
- Canadian Clinical Practice Guidelines
- US Clinical Trials
- Databases (free)
- Internet Search
- Open Access Journals.

Organizations

National Cancer Institute http://www.cancer.gov/ .

APPENDIX 2: SELECTION OF PUBLICATIONS



APPENDIX 3: INCLUDED PRIMARY STUDIES

Table 1: Included RCTs				
Study (Author, Year, and Location)	**Patient Population**	**Intervention (Type of FIT)**	**Comparator(s) (Type of gFOBT)**	**Diagnostic Performance (Or Other Specified Outcome of Interest) and Conclusion (95% CI)**
Hol et al.(2009),[11] Netherlands	10,011 patients, range 50 to 74 years of age, average risk	OC-Sensor Micro	Hemoccult II	*gFOBT:* PR 2.8% (2.2% to 3.6%) DR-CRC 0.3% (0.1% to 0.6%) DR-AN 1.2% (0.8% to 1.7%) PPV-CRC 10% (4% to 20%) PPV-AN 45% (33% to 58%) SP-CRC 97.6% (94.8% to 98.9%) SP-AN 98.5% (97.9% to 99.0%) *FIT (50 ng/mL):* PR 8.1% (7.2% to 9.1%) DR-CRC 0.5% (0.3% to 0.9%) DR-AN 3.2% (2.6% to 3.9%) PPV-CRC 7% (4% to 11%) PPV-AN 42% (36% to 49%) SP-CRC 92.9% (88.8% to 95.5%) SP-AN 95.5% (94.5% to 96.3%) *FIT (75 ng/mL):* PR 5.7% (4.9% to 6.6%) DR-CRC 0.5% (0.3% to 0.9%) DR-AN 2.7% (2.2% to 3.3%) PPV-CRC 9% (5% to 14%) PPV-AN 49% (42% to 57%) SP-CRC 95.0% (91.8% to 97.0%) SP-AN 97.2% (96.5% to 97.7%) *FIT (100 ng/mL):* PR 4.8% (4.1% to 5.6%) DR-CRC 0.5% (0.3% to 0.8%) DR-AN 2.5% (2.0% to 3.1%) PPV-CRC 10% (6% to 17%)

Table 1: Included RCTs				
Study (Author, Year, and Location)	**Patient Population**	**Intervention (Type of FIT)**	**Comparator(s) (Type of gFOBT)**	**Diagnostic Performance (Or Other Specified Outcome of Interest) and Conclusion (95% CI)**
				PPV-AN 53% (45% to 61%) SP-CRC 95.8% (93.2% to 97.5%) SP-AN 97.8% (97.2% to 98.2%) *FIT (200 ng/mL):* PR 3.5% (2.9% to 4.2%) DR-CRC 0.4% (0.3% to 0.8%) DR-AN 2.1% (1.6% to 2.6%) PPV-CRC 12% (7% to 20%) PPV-AN 62% (52% to 71%) SP-CRC 97.1% (95.0% to 98.4%) SP-AN 98.8% (98.4% to 99.0%)
van Rossum et al. (2008),[12] Amsterdam	20,623 patients, range 50 to 75 years of age, average risk; asymptomatic	OC-Sensor Micro	Hemoccult II	*Specificity to detect CRC or AA:* gFOBT: 99.0% (98.9% to 99.3%) (P < 0.05) FIT*:* 97.8% (97.4% to 98.1%) *Test completion rates:* gFOBT: 46.9%; FIT: 59.6%
Federici et al. (2005),[23] Italy	7,320 patients, range 50 to 74 years of age	OC-Hemodia (interpreted using automatic optical sensor [OC-Sensor Micro])	Hemo-Fec	*Test completion rates:* gFOBT: 30.4; FIT: 35.8 RR 1.20 (1.02 to 1.44)

AA = advanced adenomas; AN = advanced neoplasia; CI = confidence interval; CRC = colorectal cancer; DR-AN = detection rate of advanced neoplasia; DR-CRC = detection rate of colorectal cancer; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; ng/mL = nanogram per milliliter; PPV = positive predictive value; PR = positivity rate; RR = relative risk; SP-CRC = specificity to detect colorectal cancer; SP-AN = specificity to detect advanced neoplasia

Table 2: Included Observational Studies				
Study (Author, Year, and Location)	**Patient Population**	**Intervention (Type of FIT)**	**Comparator(s) (Type of gFOBT)**	**Diagnostic Performance (Or Other Specified Outcome of Interest) and Conclusion (95% CI)**
Guittet et al. (2000),[13] Italy	20,322 patients, range 50 to 74 years of age, average risk	Immudia (analyzed by MagStream 1000 automated device)	Hemoccult II	*PPV for invasive cancer:* gFOBT: 6.9% (P = 0.03); FIT: 4.0% *Sensitivity ratio for invasive cancer:* 1.48 (1.16 to 1.89) favours FIT (P < 0.001) *Sensitivity ratio for high-risk adenomas:* 3.32 (2.70 to 4.97) favours FIT
Rozen et al. (2009),[14] Israel	330 patients, mean age 64.5 ± 9.8 years, above average risk	OC-Sensor Micro	Hemoccult SENSA	*Diagnosis of CRC and AAP combined:* gFOBT: Se 53.1% (35.8% to 70.4%) Sp 59.4% (53.8% to 65.0%) FIT (from higher of 2 duplicate tests): Se 68.6% (52.7% to 84.8%) Sp 91.9% (88.9% to 95.0%)
Allison et al. (2007),[15] United States	5,841 patients, more than 50 years of age, average risk	FlexSure OBT	Hemoccult SENSA	*Sensitivity for detecting distal cancer:* FIT: 81.8% (47.8% to 96.8%), gFOBT: 64.3% (35.6% to 86.0%) Combination 64.3% (35.6% to 86.0%) *Specificity for detecting distal cancer:* FIT: 96.9% (96.4% to 97.4%), gFOBT: 90.1% (89.3% to 90.8%) Combination 98.1% (97.7% to 98.4%) *Sensitivity for detecting advanced adenomas (≥ 10 mm):* FIT: 29.5% (21.4% to 38.9%) gFOBT: 41.3% (35.6% to 86.0%) Combination 22.8% (16.1% to 31.3%) *Specificity for detecting advanced adenomas (≥ 10 mm):* FIT: 97.3% (96.8% to 97.7%) gFOBT: 90.6% (89.8% to 91.4%) Combination 98.4% (98.0% to 98.7%) *Pooled sensitivities for detection of distal cancer and AA:* gFOBT: 22.8% (16.1% to 31.3%) FIT: 29.5% (21.4% to 38.9%)

Table 2: Included Observational Studies				
Study (Author, Year, and Location)	**Patient Population**	**Intervention (Type of FIT)**	**Comparator(s) (Type of gFOBT)**	**Diagnostic Performance (Or Other Specified Outcome of Interest) and Conclusion (95% CI)**
Fraser et al. (2007),[16] United Kingdom	1,124 patients, range 50 years to 69 years, participants who had gFOBT positive result and scheduled for follow-up CS	Hema-screen DEVEL-A-TAB and hema-screen SPECIFIC analyzing system	Hema-screen	*Detection of cancer and high-risk polyps:* Se 87.8% (80.1% to 92.9%) Sp 65.3% (60.6% to 69.7%) PPV 2.53 (2.19 to 2.93) NPV 0.19 (0.11 to 0.31)
Hoepffner et al. (2006),[17] Germany	387 patients, median age 51 years, 237/387 above average risk or symptomatic	Prevent ID CC	Hemoccult	*gFOBT for detection of cancer and adenomas:* Se 29.1% (19.1% to 41.1%) Sp 90.2% (84.6% to 94.3%) PPV 56.7% (39.5% to 72.9%) NPV 74.4% (67.6% to 80.3%) *FIT for detection of cancer and adenomas:* Se 59.7% (47.5% to 71.7%) Sp 94.5% (89.8% to 97.5%) PPV 82.6% (69.7% to 91.8%) NPV 84.2% (78.2% to 89.2%) *ELISA for detection of cancer and adenomas:* Se 63.8% (51.7% to 74.9%) Sp 96.3% (92.2% to 98.7%) PPV 88.4% (76.6% to 95.7%) NPV 85.9% (79.7% to 90.6%)
Smith et al. (2006),[18] Australia	2,351 patients, average 64 years of age, screening cohort (2,351 patients) of average risk, diagnostic cohort (161 patients)	InSure	Hemoccult II	*PPV for cancer and significant adenomas:* gFOBT 20.2% (CI not provided) FIT 26.0% (CI not provided) *Positivity rate for detection of cancer*: gFOBT 54.2%; FIT 87.5% *Positivity rate for detection of significant adenomas:* gFOBT 23.0%; FIT 42.6%

Table 2: Included Observational Studies				
Study (Author, Year, and Location)	**Patient Population**	**Intervention (Type of FIT)**	**Comparator(s) (Type of gFOBT)**	**Diagnostic Performance (Or Other Specified Outcome of Interest) and Conclusion (95% CI)**
	symptomatic and had been referred for CS			
Hughes et al. (2006),[20] Australia	3,358 patients, 75% of sample between ages 50 years and 69 years	InForm	Hemoccult II	*Overall participation rate:* 36.3%; FIT > gFOBT; OR 1.9 (1.6 to 2.2)

AA = advanced adenomas; AAP = advanced adenomatous polyps; CI = confidence interval; CRC = colorectal cancer; CS = colonoscopy; ELISA = enzyme-linked immunosorbent assay; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value; Se = sensitivity; Sp = sp