

# Fecal Occult Blood Test for Colorectal Cancer Screening

An Evidence-Based Analysis

*Presented to the Ontario Health Technology  
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## **Contact Information**

The Medical Advisory Secretariat  
Ministry of Health and Long-Term Care  
20 Dundas Street West, 10th floor  
Toronto, Ontario  
CANADA  
M5G 2N6  
Email: [MASinfo.moh@ontario.ca](mailto:MASinfo.moh@ontario.ca)  
Telephone: 416-314-1092

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The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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# List of Abbreviations

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<b>AUC</b>	Area under the curve
<b>CI</b>	Confidence interval(s)
<b>CRC</b>	Colorectal cancer
<b>DCBE</b>	Double-contrast barium enema
<b>FOBT</b>	Fecal occult blood test
<b>gFOBT</b>	Guaiac fecal occult blood test
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>iFOBT</b>	Immunochemical fecal occult blood test
<b>MAS</b>	Medical Advisory Secretariat
<b>OR</b>	Odds ratio
<b>OHTAC</b>	Ontario Health Technology Advisory Committee
<b>RCT</b>	Randomized controlled trial
<b>RR</b>	Relative risk
<b>SD</b>	Standard deviation
<b>SROC</b>	Summary receiver operating characteristic

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# Executive Summary

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The colorectal cancer (CRC) screening project was undertaken by the Medical Advisory Secretariat (MAS) in collaboration with the Cancer Care Ontario (CCO).

In November 2007, the Ontario Health Technology Advisory Committee (OHTAC) MAS to conduct an evidence-based analysis of the available data with respect to colorectal cancer diagnosis and prevention. The general purpose of the project was to investigate the effectiveness, cost effectiveness, and safety of the various methods and techniques used for colorectal cancer screening in average risk people, 50 years of age and older.

The options currently offered for colorectal cancer screening were reviewed and five technologies were selected for review:

- Computed tomographic (CT) colonography
- Magnetic resonance (MR) colonography
- Wireless capsule endoscopy (PillCam Colon)
- Fecal occult blood test (FOBT)
- Flexible sigmoidoscopy

In this review, colonoscopy was considered as the “gold standard” technique by which the effectiveness of all other modalities could be evaluated. An economic analysis was also conducted to determine cost-effectiveness of different screening modalities.

Evidence-based analyses have been prepared for each of these technologies, as well as summary document that includes an economic analysis, all of which are presented at the MAS Web site: [http://www.health.gov.on.ca/english/providers/program/mas/tech/tech\\_mn.html](http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html)

## Objective

The objective of this evidence review is to examine the effectiveness and cost-effectiveness of fecal occult blood testing (FOBT), including guaiac FOBT (gFOBT) and immunochemical FOBT (iFOBT), for use in colorectal cancer (CRC) screening in asymptomatic, average-risk adults.

Specifically:

- Is the use of gFOBT or iFOBT associated with a reduction in CRC and overall mortality?
- What are the sensitivity and specificity of gFOBT and iFOBT for the detection of 1) CRC and 2) large polyps ( $\geq 1$  cm)?

## Clinical Need

CRC is the most common cause of non-tobacco related cancer death in Canada. It has been estimated that in 2007, 7,800 people were diagnosed with CRC in Ontario and 3,250 died from the disease, making the province’s incidence and mortality rate of CRC amongst the highest in the world.



## **Description of Technology/Therapy**

There are two general types of FOBT that are categorized according to the analyte detected: guaiac FOBT (gFOBT) and immunochemical FOBT (iFOBT). Blood in the stool is a nonspecific finding but may originate from CRC or larger (>1 cm) polyps (small adenomatous polyps do not tend to bleed). Bleeding from cancers and larger polyps may be intermittent and not always detectable in a single sample. The FOBT thus requires regular testing that consists of collecting specimens from consecutive bowel movements. A positive gFOBT or iFOBT involves a diagnostic workup with colonoscopy to examine the entire colon in order to rule out the presence of cancer or advanced neoplasia.

## **Methods of Evidence-Based Analysis**

A literature search was conducted from January 2003 to June 2008 that included OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), The Cochrane Library, and the International Agency for Health Technology Assessment/Centre for Review and Dissemination.

### **Inclusion Criteria**

- Patients at average risk for CRC
- All patients must be at least 50 years of age
- Biennial FOBT as a screening modality and use of colonoscopy as the reference standard
- Systematic reviews and randomized controlled trials (RCTs)
- Outcomes: CRC mortality, overall mortality, sensitivity, specificity, adverse effects

### **Exclusion Criteria**

- Studies involving fewer than 100 patients
- Studies that do not report sufficient data for analysis

### **Comparisons of Interest**

Evidence exists for these comparisons of interest:

- gFOBT compared with the reference “gold standard” colonoscopy (or double-contrast barium enema where colonoscopy is incomplete or contraindicated)
- iFOBT compared with the reference gold standard colonoscopy (or DCBE where colonoscopy is incomplete or contraindicated)
- gFOBT compared with iFOBT

The quality of the diagnostic studies was examined according to the ‘GRADE Working Group criteria’ for grading quality of evidence and strength of recommendations for diagnostic tests and strategies.

## Summary of Findings

### Single-Test Studies

There is limited direct/indirect evidence that iFOBT has sensitivity/specificity superior to that of unhydrated gFOBT for CRC detection:

- sensitivity for gFOBT: 13% and 25%
- pooled iFOBT sensitivity: 81%

There is evidence that iFOBT and gFOBT have lower sensitivities for adenoma detection than for CRC detection:

- sensitivity for rehydrated gFOBT 22%
- pooled iFOBT sensitivity 28%

### Repeated-Test Studies

No trials have examined CRC mortality outcomes after repeated testing of iFOBT.

Two RCTs from the United Kingdom and Denmark showed significant reduction in CRC mortality using unhydrated gFOBT biennially

- Relative risk reductions of 13% (UK trial) and 16% (Danish trial); absolute difference of 0.1% (UK trial) and 0.2% (Danish trial).
- No significant reduction in overall mortality

Interval cancers (CRC that develop in the intervals between routine screening)

- United Kingdom trial: 236 CRCs detected by positive test, 236 interval CRCs after negative test
- Danish trial : 120 CRCs detected by positive test, 146 interval CRCs after negative test

Unhydrated gFOBT has low sensitivity for CRC detection (45% in the UK trial and 54% in the Danish trial).

- true positive rate 50% (United Kingdom and Danish RCTs)
- false positive rate 5%–10%
- true negative rate 90%–95% (from observational studies as RCTs did not report specificity)
- false negative rate 50%

**ES Table 1: Guaiac FOBT – GRADE Quality of Evidence for Interventions**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
CRC Mortality	RCT Danish N = 137,485 United Kingdom N = 152,850	No serious limitations	Yes (RR reduction in 2 trials 13% and 16%; absolute difference 0.1% and 0.2% respectively).	Age range Danish and United Kingdom study 45–75 years*	High

CRC indicates colorectal cancer; FOBT, fecal occult blood test; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

\*Unlikely to be an important uncertainty.

**ES Table 2: GRADE Quality of Evidence for Diagnostic Tests: Implications of Testing Focusing on Accuracy**

New Test and Reference Test	Putative Benefit	Diagnostic Accuracy		Patient Outcomes and Expected Impact on Management			
		Sensitivity	Specificity	True Positive	True Negative	False Positive	False Negative
<i>Presumed Influence on Outcomes Important to Patients</i>							
iFOBT and Colonoscopy	Simple, non-invasive	Less	Less	<ul style="list-style-type: none"> <li>Benefit from diagnosis and treatment after confirmatory colonoscopy</li> <li>Small risk of bowel perforation during colonoscopy</li> </ul>	<ul style="list-style-type: none"> <li>Benefit of reassurance</li> </ul>	<ul style="list-style-type: none"> <li>Anxiety/worry leading up to confirmatory colonoscopy</li> <li>Small risk of bowel perforation during confirmatory colonoscopy</li> </ul>	<ul style="list-style-type: none"> <li>Detriment from delayed diagnosis</li> </ul>
<i>Directness of Evidence (Test Results) for Outcomes Important to Patients</i>							
				<ul style="list-style-type: none"> <li>Some uncertainty (until after confirmatory colonoscopy)</li> </ul>	<ul style="list-style-type: none"> <li>No uncertainty</li> </ul>	<ul style="list-style-type: none"> <li>Uncertainty.</li> </ul>	<ul style="list-style-type: none"> <li>Uncertainty</li> </ul>

FOBT indicates fecal occult blood test; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

**ES Table 3: Immunochemical FOBT – GRADE Quality of Evidence for Diagnostic Studies**

No. of Studies	Design	Limitations	Indirectness	Inconsistency	Imprecise data	Quality
6	Diagnostic cohort (single test)  (reference standard for positive and negative iFOBT results was colonoscopy)	No serious limitations	<b>TP</b> Some uncertainty*§ <b>TN</b> No uncertainty <b>FP</b> Uncertainty†§ <b>FN</b> Uncertainty‡§  TP rate = 69% TN rate = 94% FP rate = 6% FN rate = 30% (from direct comparison study)	Diagnostic cohort iFOBT sensitivities: 50% to 90%	High I <sup>2</sup> in pooled sensitivity and specificity     Wide range in confidence intervals in direct comparison study	Low

\*FN indicates false negative; FOBT, fecal occult blood test; FP, false positive; Development and Evaluation; TN, true negative; TP, true positive.

\*Uncertainty until after confirmatory colonoscopy

†Stress/worry for patient until confirmatory colonoscopy

§For these 3 reasons, downgrade quality from High to Moderate.

‡Detrimental effects due to delayed diagnosis.

|| For these 3 reasons, downgrade quality from Moderate to Low.

## Considerations for the Ontario Health System

Executive Summary Table 4 shows the potential system pressures and benefit/risk analysis for the use of FOBT and colonoscopy to screen for CRC in average-risk adults, ages 50 and over in Ontario.

**ES Table 4: Summary of Potential System Pressures for FOBT Screening**

Criterion	Colonoscopy	FOBT
Primarily prevent or detect cancer?	<ul style="list-style-type: none"> <li>Prevent and detect</li> </ul>	<ul style="list-style-type: none"> <li>Detect</li> </ul>
Frequency of screening	<ul style="list-style-type: none"> <li>Every 10 years</li> <li>Must repeat at regular intervals</li> </ul>	<ul style="list-style-type: none"> <li>Every 2 years</li> <li>Must repeat at regular intervals</li> </ul>
Level of evidence	<ul style="list-style-type: none"> <li>Observational studies</li> </ul>	<ul style="list-style-type: none"> <li>RCTs</li> </ul>
Benefits	<ul style="list-style-type: none"> <li>Used as gold standard in studies</li> </ul>	<ul style="list-style-type: none"> <li>Intervention GRADE quality: High (gFOBT)</li> <li>Diagnostic GRADE quality: Low (iFOBT)</li> <li>No RCTs examining the effectiveness of repeated iFOBT on CRC mortality reduction were identified</li> <li>Limited direct/indirect evidence that iFOBT has superior sensitivity/specificity to unhydrated gFOBT for detection of CRC</li> </ul>
Risks	<ul style="list-style-type: none"> <li>0.1% risk of serious bleeding and perforation requiring surgery</li> <li>0.3% risk of serious complications (stroke/bleeding requiring hospitalization/myocardial infarction)</li> </ul>	<ul style="list-style-type: none"> <li>High interval cancer rate</li> <li>The small benefit in CRC mortality reduction (absolute difference 0.1% to 0.2%) also coincides with a 0.3% risk of serious complications.</li> </ul>
Preparation requirements	<ul style="list-style-type: none"> <li>No food 1 day prior to exam</li> <li>Office/hospital visit</li> <li>Complete bowel preparation</li> <li>Sedation</li> </ul>	<ul style="list-style-type: none"> <li>Eliminate citrus fruit and juices and vitamin C from diet for 3 days prior to/during stool collection.</li> <li>Person applies 2 samples per bowel movement (each occurring on 3 different days) onto test areas of FOBT cards.</li> </ul>
Resources required for screening asymptomatic, average-risk adults ≥ 50 years	<ul style="list-style-type: none"> <li>Increased demand for colonoscopies and colonoscopists or nurses who perform colonoscopies.</li> </ul>	<ul style="list-style-type: none"> <li>Patient receives kit from family physician, pharmacist</li> <li>Patients mail completed FOBT kit to participating laboratory</li> <li>Results sent back to patient</li> <li>Increased demand for colonoscopies for positive patients</li> </ul>
Screening test (positive)	<ul style="list-style-type: none"> <li>Removal of polyp during colonoscopy or surgery</li> </ul>	<ul style="list-style-type: none"> <li>Referral to colonoscopy</li> </ul>
Cost-effectiveness	<ul style="list-style-type: none"> <li>Cost-effective</li> </ul>	<ul style="list-style-type: none"> <li>Cost-effective</li> </ul>
Patient preference	<ul style="list-style-type: none"> <li>2nd of 5 choices in a patient survey study</li> </ul>	<ul style="list-style-type: none"> <li>5th of 5 choices in a patient survey study</li> </ul>

FOBT indicates fecal occult blood test;; gFOBT, guaiac FOBT; GRADE, Grading of Recommendations Assessment, Development and Evaluation; iFOBT, immunochemical FOBT; RCT, randomized controlled trial.

# Background

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The colorectal cancer (CRC) screening project was undertaken by the Medical Advisory Secretariat (MAS) in collaboration with the Cancer Care Ontario (CCO).

In November 2007, the Ontario Health Technology Advisory Committee (OHTAC) MAS to conduct an evidence-based analysis of the available data with respect to colorectal cancer diagnosis and prevention. The general purpose of the project was to investigate the effectiveness, cost effectiveness, and safety of the various methods and techniques used for colorectal cancer screening in average risk people, 50 years of age and older.

The options currently offered for colorectal cancer screening were reviewed and five technologies were selected for review:

- Computed tomographic (CT) colonography
- Magnetic resonance (MR) colonography
- Wireless capsule endoscopy (PillCam Colon)
- Fecal occult blood test (FOBT)
- Flexible sigmoidoscopy

In this review, colonoscopy was considered as the “gold standard” technique by which the effectiveness of all other modalities could be evaluated. An economic analysis was also conducted to determine cost-effectiveness of different screening modalities.

Evidence-based analyses have been prepared for each of these technologies, as well as summary document that includes an economic analysis, all of which are presented at the MAS Web site:

[http://www.health.gov.on.ca/english/providers/program/mas/tech/tech\\_mn.html](http://www.health.gov.on.ca/english/providers/program/mas/tech/tech_mn.html)

## Objective

The objective of this evidence review is to examine the effectiveness and cost-effectiveness of fecal occult blood testing (FOBT), including guaiac FOBT (gFOBT) and immunochemical FOBT (iFOBT), for use in colorectal cancer (CRC) screening in asymptomatic, average-risk adults.

## Clinical Need: Target Population and Condition

CRC is the most common cause of non-tobacco related cancer death in Canada. It has been estimated that in 2007, 7,800 people were diagnosed with CRC in Ontario and that 3,250 died from the disease, making the province’s incidence and mortality rate of CRC amongst the highest in the world. (1) Screening tests for people at average risk for CRC (i.e. asymptomatic,  $\geq 50$  years of age, and with no other risk factors for CRC) fall into two categories. The first of these is comprised of the partial and full structural exams (e.g. flexible sigmoidoscopy and colonoscopy), which aim to detect cancer and premalignant adenomatous polyps. In the second category there is FOBT, which is intended to detect CRC at earlier (and potentially more easily curable) stages. Prevention is both limited and incidental and is not the primary goal of FOBT.

According to the American Gastroenterological Association, CRC prevention should be the primary goal of screening. (2) These tests include partial or full structural exams and require bowel preparation and an office or hospital visit. Any positive finding determined via a non-colonoscopy technique requires follow-up with colonoscopy. Some patients may prefer, however, to be screened in the privacy of their home or they may not have access to such invasive tests. Collection of fecal samples can be performed at home without bowel preparation. Yet FOBT is less likely to prevent cancer compared with invasive tests and must be repeated at regular intervals and if the test is abnormal, colonoscopy is still required. (2)

## **Fecal Occult Blood Testing**

There are two general types of FOBT that are categorized according to the analyte detected: guaiac FOBT (gFOBT) and immunochemical FOBT (iFOBT) (summarized in Table 1). Blood in the stool is a nonspecific finding but may originate from CRC or larger (>1 cm) polyps (small adenomatous polyps do not tend to bleed). Bleeding from cancers and larger polyps may be intermittent and not always detectable in a single sample. FOBT thus requires regular testing that consists of collecting specimens from consecutive bowel movements. A positive gFOBT or iFOBT involves a diagnostic workup with colonoscopy to examine the entire colon in order to rule out the presence of cancer or advanced neoplasia. (2)

A meta-analysis by Pignone et al. (3) compared gFOBT positivity rates in people who completed a gFOBT with or without dietary restrictions (four RCTs and a quasi-randomized study). Dietary restrictions varied in duration (24 or 48 hours before testing, or only during testing) and in the foods that were restricted, but all dietary restrictions included no red meat. Four of the studies restricted certain vegetables before and during testing and two studies restricted vitamin C and aspirin intake. The authors' meta-analysis found no difference in the summary positivity rate between those assigned to dietary restrictions versus those not restricted. (3)

A study from the United Kingdom reported on samples collected from three people consuming various amounts of vitamin C. (4) There was no evidence to indicate that a normal level of vitamin intake (75–90 mg per day, the recommended daily allowance) interferes with gFOBT results. The study concluded that the limit of 250–500 mg per day in intake of vitamin C as recommended in many of the package insert instructions for gFOBT is appropriate. (4)

## **Regulatory Status**

Five gFOBTs and six iFOBTs are licensed by Health Canada (see Table 2).

**Table 1: Characteristics of the Guaiac and Immunochemical Fecal Occult Blood Tests\***

	<b>gFOBT</b>	<b>iFOBT</b>
Procedure	Person applies 6 fecal samples (2 samples from each of 3 consecutive spontaneous passed stools) onto test areas of FOBT cards	In general, similar to gFOBT
Mechanism of action	Oxidation of guaiac, which is pre-inserted on the card, by hydrogen peroxide catalyzed by the peroxidase activity of hemoglobin	Uses antibodies against human globin; does not rely on peroxidase
Specific for human hemoglobin	Detects peroxidase in human blood as well as peroxidase in dietary constituents such as rare red meat and some fruit and vegetables	Yes – detects globin Globin is degraded by digestive enzymes in the upper gastrointestinal tract – therefore iFOBT is specific for bleeding in colon and rectum
Special drug/dietary restrictions before test	Manufacturers generally state to avoid red meats and raw fruits and vegetables that contain peroxidase-like substances 2–3 days before and during stool collection.  High-dose vitamin C supplementation may block the peroxidase reaction and create false negative results.	No
Requirement for colonoscopy after positive finding	Yes	Yes

\*FOBT indicates fecal occult blood test.

**Table 2: Fecal Occult Blood Tests Licensed by Health Canada**

<b>gFOBT</b>	<b>iFOBT</b>
Hemoccult	One-Step Fecal Occult Blood Test
Hemoccult SENA	Rapid Response One-Step Fecal Occult Blood Test
ColoScreen	Tremblay-Harrison Minute Lab Fecal Occult Blood Test Device
TRI-SLIDE	Actim Fecal Blood Test
Hema Screen	Innovacon FOB One Step Fecal Occult Blood Test  Hemoccult ICT, Immunochemical Fecal Occult Blood Test

# Evidence-Based Analysis of Effectiveness

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## Research Question

What is the effectiveness and cost-effectiveness of using FOBT (gFOBT or iFOBT) in CRC screening?

Specifically

- Is the use of gFOBT or iFOBT associated with a reduction in CRC and overall mortality?
- What are the sensitivity and specificity of gFOBT and iFOBT in the detection of 1) CRC and 2) large polyps ( $\geq 1$  cm)?

## Methods

A literature search was conducted from January 2003 to June 2008 that included OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing & Allied Health Literature (CINAHL), The Cochrane Library, and the International Agency for Health Technology Assessment/Centre for Review and Dissemination.

## Inclusion Criteria

- Patients at average risk for CRC
- All patients must be at least 50 years of age
- Patients receive biennial FOBT as a screening modality and colonoscopy as the reference standard
- Systematic reviews and RCTs
- Outcomes: CRC mortality, overall mortality, sensitivity, specificity, and adverse effects

## Exclusion Criteria

- Studies with fewer than 100 patients
- Studies that did not report sufficient data for analysis

## Comparisons of Interest

Evidence exists for these comparisons of interest:

- gFOBT compared with the reference gold standard colonoscopy [or double-contrast barium enema (DCBE) where colonoscopy is incomplete or contraindicated]
- iFOBT compared with the reference gold standard colonoscopy (or DCBE where colonoscopy is incomplete or contraindicated)
- gFOBT compared with iFOBT



## Assessment of Evidence Quality

The quality of the RCTs was examined according to the GRADE Working Group criteria for interventions (5) and the quality of the diagnostic studies was examined according to the GRADE Working Group criteria for diagnostic tests. (6)

As for other interventions, the GRADE approach to grading the quality of evidence and the strength of recommendations for diagnostic tests or strategies provides a comprehensive and transparent approach for developing recommendations. (6) This strategy is summarized as:

- Cross-sectional or cohort studies can provide high-quality evidence of test accuracy. However, test accuracy is a surrogate for outcomes that are important to patients, so such studies often provide low-quality evidence for recommendations about diagnostic tests, even when the studies do not have serious limitations.
- Inferences from accuracy data that a diagnostic test or strategy improves outcomes important to patients requires the availability of effective treatment, reduction of test-related adverse effects or anxiety, or improvement in patients' well-being through the provision of prognostic information.

Judgments are needed to assess the directness of test results in relation to the consequences of diagnostic recommendations that are important to patients.

# Results of Evidence-Based Analysis

The literature search of studies published between January 2003 and June 2008 identified six systematic reviews and three RCTs. The quality of the included systematic reviews is presented below in Table 3 and the reviews are summarized by date, country, organization, and overall conclusion in Appendix 2.

**Table 3: Quality of Evidence of Included Studies**

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	6 Systematic reviews 3 RCTs
Large RCT unpublished but reported to an international scientific meeting	1(g)*	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

g refers to grey literature; RCT, randomized controlled trial.

\*For each study, the evidence level was assigned according to a ranking system based on a hierarchy proposed by Goodman. (7) The designation "g" was added for preliminary reports of studies that have been presented at international scientific meetings.

## Summary of Existing Evidence

### Systematic Reviews

The key studies included of the systematic reviews are described in the following sections, which are categorized according to whether gFOBT or iFOBT was used and whether single or repeated samples were taken.

#### *Single Testing Using gFOBT in Prospective Observational Studies*

In a review by Rabeneck et al, 13 prospective studies provided data on performance characteristics for gFOBT using a single application in an asymptomatic population (Table 4). (1) In only three studies were colonoscopies performed on all subjects; for these a more accurate determination of sensitivity and specificity was possible (Table 4). Ten of the 13 studies did not offer colonoscopy to those with a negative gFOBT. In one study that used rehydrated samples, the sensitivity for CRC detection was 50%. The two other studies that used nonrehydrated gFOBT reported sensitivities of 12.9% and 25%, and specificities of 95.2% and 80%, respectively.

**Table 4: Test Characteristics for CRC Detection Using gFOBT in Single-Testing of Asymptomatic Populations in Prospective Studies**

Study	N	Reference Standard	Rehydrated or Non-rehyd. gFOBT	Positivity, %	Sensitivity, %	Specificity, %	PPV, %
Imperiale et al., 2004*	4404	Colonoscopy	Nonrehydrated	10.8	12.9	95.2	5.5
Sung et al., 2003	505	Colonoscopy	Nonrehydrated	20	25	80	1.0
Lieberman and Weiss, 2001†	2885	Colonoscopy	Rehydrated	8.3	50	Not reported	6.5

Adapted from Rabeneck et al. (1)

gFOBT indicates guaiac fecal occult blood test; PPV, positive predictive value

\*In each study group, 14% had a family history of colorectal cancer.

†In the whole cohort, 14.2% reported having a first-degree relative with colorectal cancer.

The study by Lieberman and Weiss used colonoscopy (reference standard) to determine the prevalence of neoplasia and the sensitivity of one-time screening with rehydrated gFOBT plus sigmoidoscopy. (8) Asymptomatic patients provided stool specimens for gFOBT and then underwent colonoscopy. Sigmoidoscopy was defined as examination of the rectum and sigmoid colon during colonoscopy, and sensitivity was estimated by determining how many patients had advanced neoplasia (defined as an adenoma 1 cm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or an invasive cancer).

Of the patients with advanced neoplasia, 23.9% had a positive test for occult blood. Compared with those who had negative tests for FOBT, the relative risk (RR) of advanced neoplasia in people who had a positive test was 3.5 (95% CI, 2.8–4.4). Sigmoidoscopy identified 70% of all patients with advanced neoplasia, while combined FOBT and sigmoidoscopy identified 75.8% of people with advanced neoplasia. Lieberman and Weiss concluded that one-time screening with both gFOBT (rehydrated) and sigmoidoscopy fails to detect advanced colonic cancer in 24% of patients with the condition.

### ***Repeated gFOBT in Randomized Controlled Trials***

Hewitson et al. (9) conducted an updated Cochrane systematic review to determine whether screening for CRC using FOBT (specifically Hemoccult) reduces CRC mortality and to consider the benefits, harms, and potential consequences of screening. By way of a literature search, conducted from January 1989 to February 2006, the authors identified four RCTs (10-13) that were reported in 11 published articles. These trials comprised 327,043 people across four countries with follow-up ranging from 8 to 18 years. (13) Three of the RCTs used colonoscopy as the main reference standard but in the fourth, a Swedish RCT, flexible sigmoidoscopy and DCBE was used as the reference standard. This RCT was thus excluded from the Cochrane analysis by the Medical Advisory Secretariat.

The primary analysis of the Cochrane review used ‘intention to screen’ and a secondary analysis adjusted for nonattendance. The characteristics of the RCTs included in the study are shown in Table 5. Three trials performed biennial screening, while the three-arm Minnesota trial evaluated both annual and biennial screenings.

**Table 5: Description of RCTs of FOBT**

Location	Age Range, Years	Screening Frequency	Follow-up Duration, years	No. of Screening Rounds	Attending First Screening, %	At Least 1 Round, %
England	45–74	Biennial	11.7	6	53.4	59.6
Denmark	45–75	Biennial	17	9	66.8	NR
United States	50–80	Biennial	18	6	NR	78.0

NR indicates not reported.

Only those participants with a positive gFOBT were offered colonoscopy; negative gFOBT results were not confirmed with colonoscopy. All three trials employed adequate randomization procedures resulting in comparable study groups. Blinding of the participants to the intervention was not possible. Mortality analyses were by intention to treat in the Funen, Minnesota, and Nottingham trials. (10;11;13) Blinded standardized assessment for mortality was performed for all three RCTs. The Funen trial included deaths from CRC treatment complications in the CRC mortality analyses; this was not specifically stated for the other trials.

Compliance for screening was higher for the Minnesota trial than for the European trials. In most trials, Hemoccult screening continued to be offered to all screening participants regardless of previous attendance. In the Funen study, however, only those people who participated in the first round of screening were invited to subsequent screening rounds; therefore, compliance with testing was very high (91%–94%). This could affect the generalizability of the results for the Funen study.

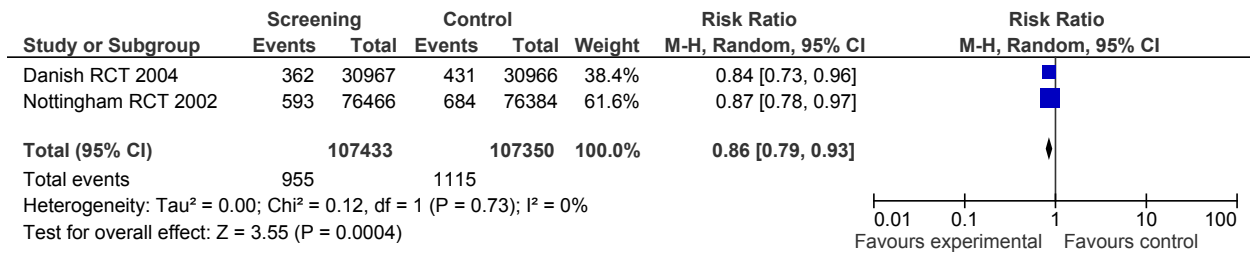
The compliance rate for attending all biennial screening rounds was 60% in the Minnesota trial (at the 13-year follow-up) (10), 44% in the Danish trial (8558/19654 alive at the 17-year follow-up) (14), and 57% in the United Kingdom trial (at the 11-year follow-up) (15).

### ***Meta-Analysis of CRC Mortality***

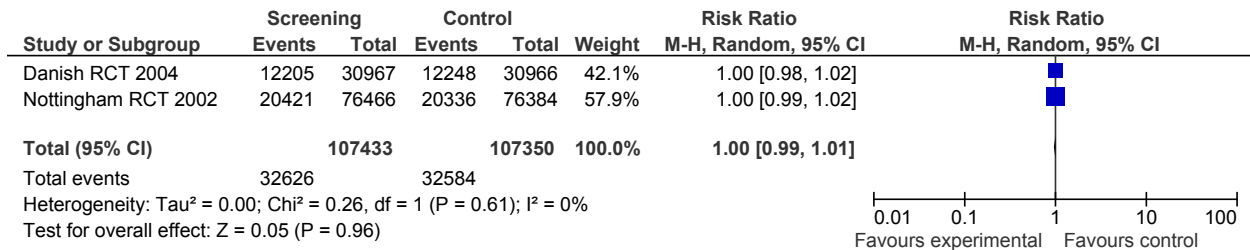
The Medical Advisory Secretariat performed new meta-analyses excluding the Goteborg trial as it did not use colonoscopy as the reference standard and the biennial Minnesota trial because it used rehydrated gFOBT. As part of a sensitivity analysis, additional meta-analyses examined the effect of pooling trials that used both nonrehydrated and rehydrated gFOBT.

As shown in Figure 1, combining trials that used only biennial screening (Funen, Minnesota, Nottingham) showed a 14% relative reduction in CRC mortality (RR, 0.86 [95% CI, 0.79–0.93]). There was no significant difference in all-cause mortality and non-CRC mortality (see Figures 2 and 3).

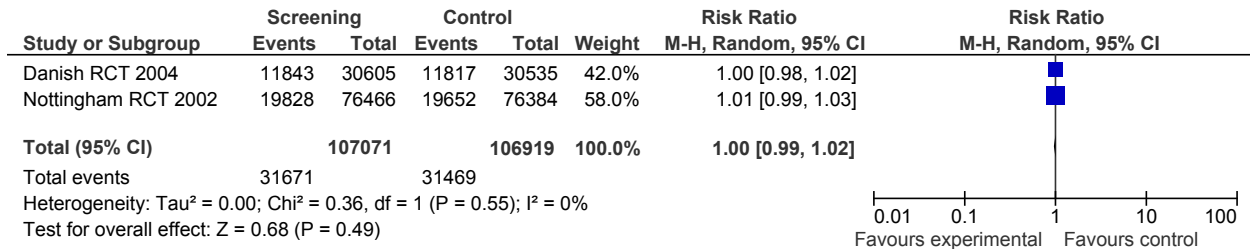
When the trials that examined nonrehydrated and rehydrated gFOBT were pooled, their results were found to be similar to the nonrehydrated gFOBT summary statistics. There was a significant reduction in CRC mortality (see Figure 4) but no significant reduction in all-cause or non-CRC mortality (see Figures 5 and 6).



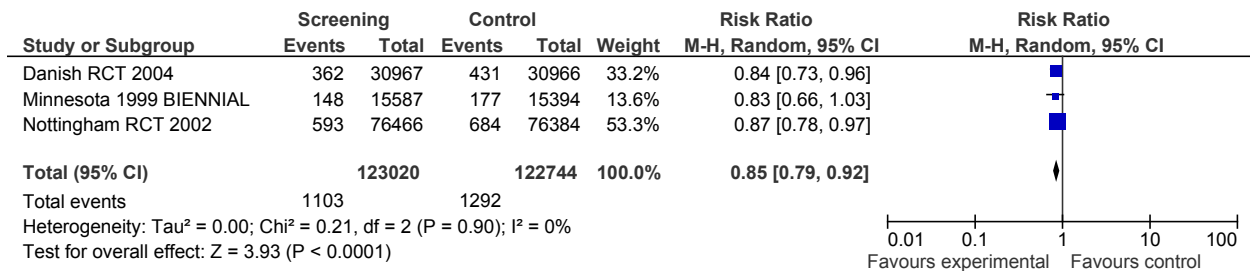
**Figure 1: Nonrehydrated gFOBT Compared With Control (No Screening), CRC Mortality**



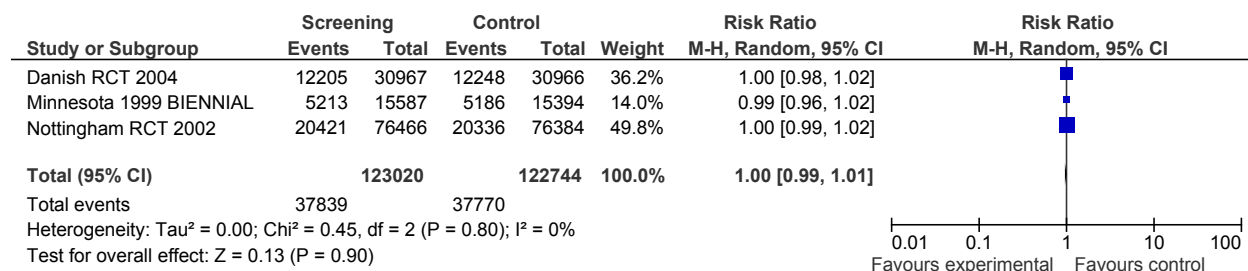
**Figure 2: Nonrehydrated gFOBT Compared With Control (No Screening), All-Cause Mortality**



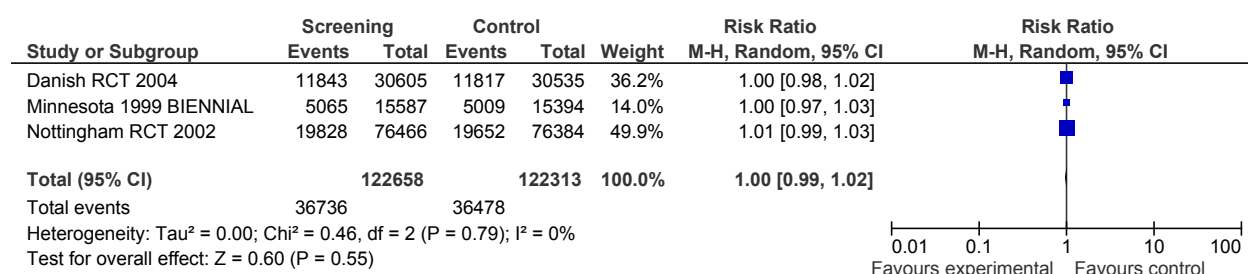
**Figure 3: Nonrehydrated gFOBT Compared With Control (No Screening), Non-CRC Mortality**



**Figure 4: Nonrehydrated and Rehydrated gFOBT Compared With Control Groups, CRC Mortality**



**Figure 5: Nonrehydrated and Rehydrated gFOBT Compared With Control Groups, All-Cause Mortality**



**Figure 6: Nonrehydrated and Rehydrated gFOBT Compared With Control Groups, Non-CRC Mortality**

### Accuracy of gFOBT in RCTs

Sensitivity, specificity, and PPV were estimated for the RCTs because not all participants were offered colonoscopies. (1) In these studies, only those with a positive gFOBT were offered any follow-up evaluation; the number of false negatives could not be calculated as participants with a negative FOBT did not have their test results confirmed by colonoscopy.

Two approaches were used to define sensitivity.

1. The Funen and Nottingham trials used the definition:

**sensitivity = true positives/(true positives + false negatives)** where, for a true positive, FOBT detects the cancer, and for a false negative, those with a negative screen had a CRC detected between screening rounds or during follow-up after the last screening round.

In studies that used this approach, the sensitivity of gFOBT for CRC detection CRC ranged from 45% to 54%.

2. For the Minnesota study, the cancers diagnosed in the first year after screening were included as:

**sensitivity = true positives/(true positives+ false negatives)**, where true positives were CRCs discovered within a year of a positive FOBT result and false negatives were those CRCs discovered within a year of a negative FOBT result. The sensitivity for CRC detection for annual and biennial screening in this study was found to be 80.8% and 92.2% , respectively, while for specificity it was found to be 97.7% and 90.4%.

The Canadian Task Force on Preventive Health Care recalculated the sensitivity for the Minnesota trial, using a definition of ‘**the number of cancers detected through screening divided by the total number of cancers**’. (16) Under these terms, the result was 38.3% for biennial rehydrated gFOBT. The Task Force also calculated the sensitivity for the Danish study (it did not report sensitivity) as 48% for biennial testing. The sensitivities and specificities, all calculated the same way, are summarized in Table 6; sensitivities for the Funen and Minnesota trial are recalculated by The Canadian Task Force on Preventive Health Care. (16)

**Table 6: gFOBT in Biennial Screening: Sensitivity for CRC**

RCT	Rehydrated	Follow-up, years	Sensitivity, %
Nottingham	No	10	54
Funen	No	10	45
Minnesota	83% rehydrated	13	38

RCT indicates randomized controlled trial.

### *Adverse Events*

Three studies describe psychological morbidity related to gFOBT. (17-19). In the first of these, Lindholm et al. investigated the degree of worry among people invited to participate in the Goteborg RCT. (17) Telephone interviews were carried out within a subset of those who had a positive gFOBT. Nineteen percent (49/257 people) reported severe worry before they received the result of the first test. Eighteen percent of people (28/156) reported that their daily life was negatively affected to some extent before they received the result of the first test. This increased to 38% (59/156) among those who had a positive first test and was about the same (42% or 25/60) for those in whom the second test was also positive. This worry disappeared after endoscopy in most of the people (67% or 40/60); however, it was still pronounced after endoscopy in 6 of the 60 patients.

Mant et al. examined the concern of patients with false positive results from gFOBT who participated in a RCT in the United Kingdom that investigated compliance with different methods of CRC screening. (18) Of 56 patients with false positive result, 54 agreed to be interviewed. An age- and sex-matched control group of 112 people with negative test results was identified and 92 (82%) returned the questionnaires. Thirty-seven (68.5%) of the patients with false positive results felt some degree of distress and, of these, 62% were slightly distressed, 24% moderately distressed, and 14% very distressed. Sixty-nine percent of patients with false positive results reported being worried that they might have cancer and, of these, 68% reported being slightly distressed, 24% moderately distressed, and 8% very distressed.

Finally, Parker et al. evaluated adverse psychological effects associated with FOBT in a subset of people from two different general practices participating in the Nottingham trial. (19) From the study population (N = 152,850), a general health questionnaire was sent to 2,184 people before screening and 1,693 after screening. Among the 843 people who completed both questionnaires, there was no significant difference in the proportion scoring 5 or more (which was considered to indicate probable psychiatric morbidity) before and 3 months after the offer of a gFOBT test. Anxiety scores were measured in 100 gFOBT-positive patients and were highest after notification of a positive gFOBT and before investigation by colonoscopy. In patients with false positive results, scores fell the day after colonoscopy and remained low 1 month later.

### Single Testing Using iFOBT in Observational Studies

For the analysis by the Medical Advisory Secretariat, only cohort studies using colonoscopy as the reference standard for both positive and negative iFOBT results were examined. It should be noted that no RCTs that examined screening for CRC using iFOBT were identified.

### Sensitivity and Specificity of iFOBT for Detection of CRC

Six cohort studies were identified (20-25) for which the pooled sensitivity of iFOBT for the detection of CRC was 0.81 (95% CI, 0.74–0.87) (see Figure 7). The pooled specificity of iFOBT for detection of CRC was 0.94 (95% CI, 0.94–0.95) (see Figure 8). For both of the pooled results, there was significant heterogeneity.

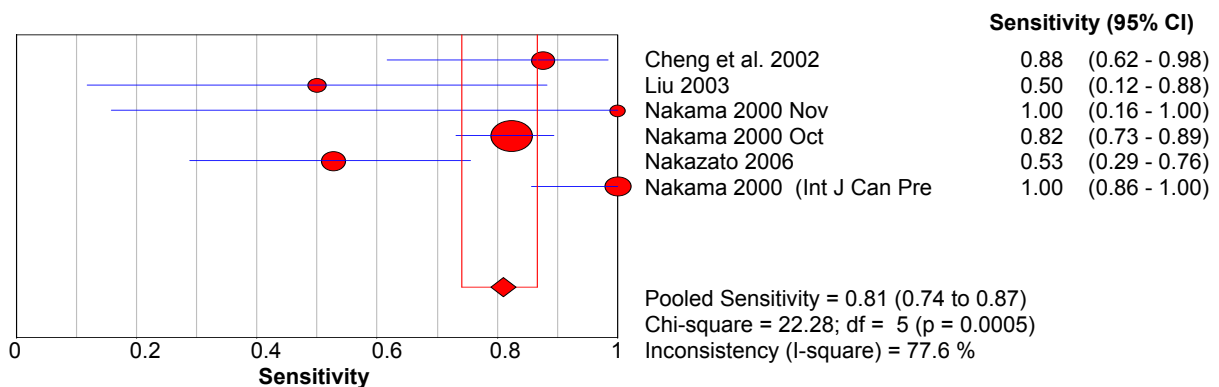


Figure 7: Sensitivity of iFOBT for CRC Detection

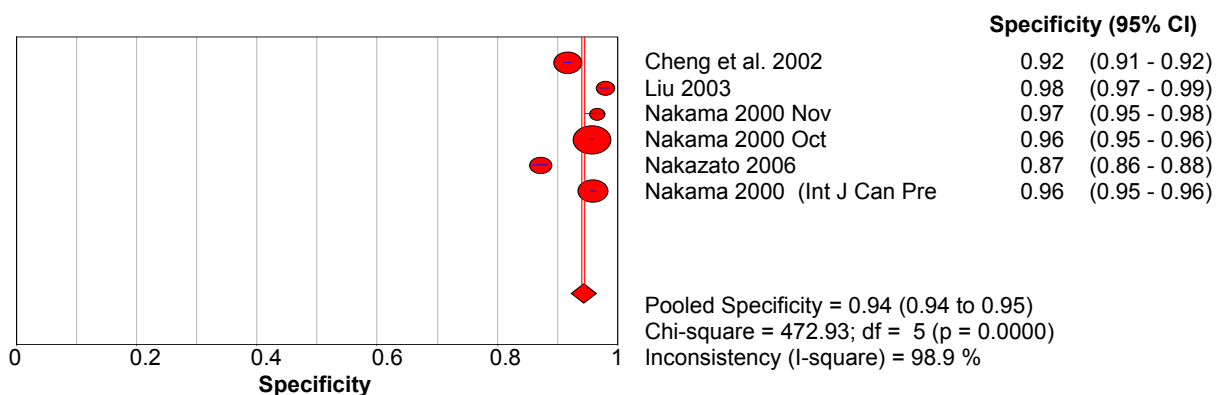


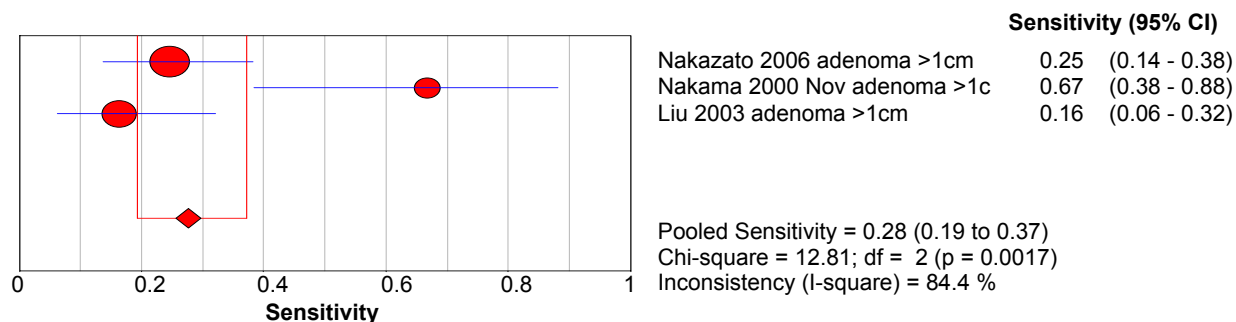
Figure 8: Specificity of iFOBT for CRC Detection

### Sensitivity and Specificity of iFOBT for Adenoma ( $\geq 1$ cm) Detection

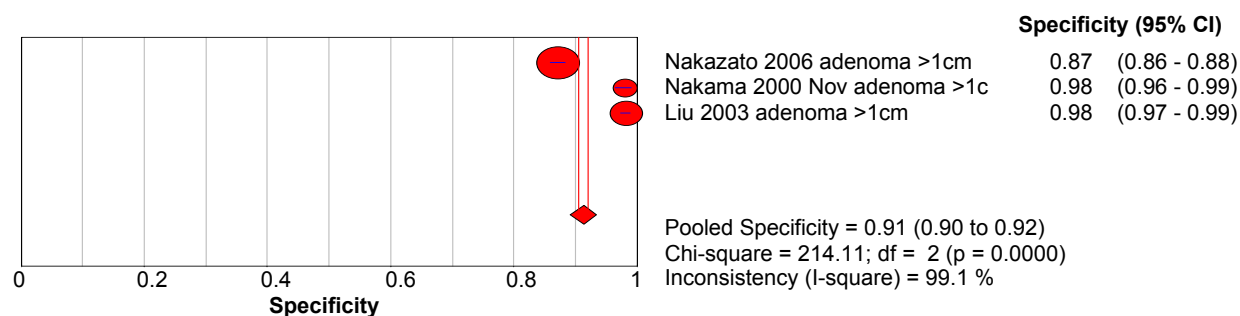
Three cohort studies were identified (21;23;25) for which the pooled sensitivity of iFOBT for the detection of adenomas  $\geq 1$  cm was 0.28 (95% CI, 0.19–0.37) (see Figure 9). The pooled specificity of iFOBT for detection of adenomas  $\geq 1$  cm was 0.91 (95% CI, 0.90–0.92) (see Figure 10). Again, there was significant heterogeneity in the pooled results for both sensitivity and specificity.



Overall, the pooled sensitivity and specificity for detection of adenomas  $\geq 1$  cm were less than the pooled sensitivity and specificity for the detection of CRC.



**Figure 9: Sensitivity of iFOBT for the Detection of Adenomas  $\geq 1$  cm**



**Figure 10: Specificity of iFOBT for the Detection of Adenomas  $\geq 1$  cm**

### *Direct Comparison of gFOBT and iFOBT*

One cohort study (N = 8,104) directly evaluated gFOBT (unrehydrated and rehydrated) and iFOBT using colonoscopy and follow-up as the reference standard after a positive FOBT, and referral to a cancer registry and follow-up after a negative FOBT. (26) The sensitivity for the detection of cancer or polyps  $\geq 1$  cm using iFOBT [68.8% (95% CI, 51.1–86.4) and 66.7% (95% CI, 57.0–76.3), respectively] was higher than the sensitivity for the detection of cancer or polyps  $\geq 1$  cm using unrehydrated gFOBT [37.1% (95% CI, 19.7–54.6) and 30.8% (95% CI, 21.6–40.1), respectively].

### **Patient Preferences for CRC Screening**

Marshall et al. examined patient preferences for CRC screening modalities and uptake rates using utility-based methods. (27) A survey was mailed to a random sample of Canadians aged 40 to 60 years from a primary care network. Of the 1,047 surveys mailed, 547 were returned and approximately 30% of respondents preferred no screening. Accuracy-related test attributes were more important than attributes related to test process. The most preferred attribute was 90% sensitivity (choices of 90%, 70%, or 40%), followed by 100% specificity (choices of 100%, 80%, or 50%), no preparation (choices of special diet, laxatives, or none), process (CT scan, stool, scope, or barium enema) and no pain (choices of mild or none). (27)

Based on choice probabilities of CRC screening modalities, virtual colonoscopy was the most preferred screening test, followed by colonoscopy, DCBE, sigmoidoscopy, fecal DNA testing, and FOBT. The ordering of preference for the alternative CRC screening modalities was driven primarily by the estimates of accuracy (sensitivity and specificity). (27) The model results were then used to predict the expected uptake rates for CRC screening programs that offered different mixes of alternative CRC screening techniques. Assuming that CRC screening uptake would be 30% if FOBT were the only screening test available, adding one of the other screening tests would increase uptake by a percent change of 24% to 30% (i.e., by 7.2 to 9 percentage points). The greatest impact on screening uptake, a 42% relative increase, would be achieved if the program made available all the common approaches to CRC screening (i.e. FOBT, DCBE, sigmoidoscopy, and colonoscopy) rather than FOBT alone. If all common approaches for CRC screening were available, and virtual colonoscopy or fecal DNA testing were introduced, the increment in CRC screening uptake would be approximately 2%. (27) Marshall et al. concluded that there is a need to consider patient preferences (including no screening) and choice regarding alternative screening modalities in order to optimize the uptake of CRC screening. (27)

## Quality of the Evidence

Tables 7 to 9 show the quality of evidence for the use of gFOBT and iFOBT to screen average-risk adults  $\geq 50$  years for colorectal cancer according to the GRADE quality-of-evidence criteria. For CRC mortality endpoints, the GRADE criteria for assessing interventions are used and for test performance characteristics (e.g. sensitivity and specificity) the GRADE criteria for diagnostic tests were applied. (5;6)

The quality of evidence for gFOBT was found to be high (Table 7) and for iFOBT is low (Tables 8 and 9).

**Table 7: gFOBT – GRADE Evidence Quality for Interventions**

Outcome	Design	Quality	Consistency	Directness	Overall Quality
CRC Mortality	RCT Danish N = 137,485  United Kingdom N = 152,850	No serious limitations	Yes (RR reduction in 2 trials 13% and 16%; absolute difference 0.1% and 0.2% respectively)	*Age ranges of the Danish and United Kingdom studies were 45 to approximately 75 years, while Ontario program would target ages 50+	High

CRC indicates colorectal cancer; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT.

\*Unlikely to be an important uncertainty.

**Table 8: GRADE Evidence Quality for Diagnostic Tests: Implications of Testing Focusing on Accuracy**

New Test and Reference Test	Putative Benefit	Diagnostic Accuracy		Patient Outcomes and Expected Impact on Management			
		Sensitivity	Specificity	True Positive	True Negative	False Positive	False Negative
<i>Presumed Influence on Outcomes Important to Patients</i>							
iFOBT and Colonoscopy	Simple, non-invasive	Less	Less	Benefit from diagnosis and treatment after confirmatory colonoscopy	Benefit from reassurance	Anxiety/worry leading up to confirmatory colonoscopy	Detriment from delayed diagnosis
				Small risk of bowel perforation during colonoscopy		Small risk of bowel perforation during confirmatory colonoscopy	
<i>Directness of Evidence (Test Results) for Outcomes Important to Patients</i>							
				Some uncertainty (until after confirmatory colonoscopy)	No uncertainty	Uncertainty	Uncertainty

iFOBT indicates immunochemical fecal occult blood test; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

**Table 9: iFOBT – GRADE Evidence Quality for Diagnostic Studies**

No. of Studies	Design	Limitations	Indirectness	Inconsistency	Imprecise data	Quality
6	Diagnostic Cohort (single test)  (reference standard for positive and negative iFOBT results was colonoscopy)	No serious limitations	<b>TP</b> Some uncertainty* <b>TN</b> No uncertainty <b>FP</b> Uncertainty† <b>FN</b> Uncertainty‡  TP rate = 69% TN rate = 94% FP rate = 6% FN rate = 30% (from direct comparison study)	Diagnostic cohort iFOBT sensitivities: 50% to 90%. §	High I <sup>2</sup> in pooled sensitivity and specificity¶  Wide range in confidence intervals in direct comparison study.¶¶	Low

FN indicates false negative; FOBT, fecal occult blood test; FP, false positive; TN, true negative; TP, true positive.

\* Uncertainty until after confirmatory colonoscopy.

† Stress/worry for patient until confirmatory colonoscopy. ‡ Detrimental effects due to delayed diagnosis. For these reasons, downgrade from High to Moderate.

§ Wide range in sensitivities.

¶ Heterogeneity in pooled results.

¶¶ Wide range in confidence intervals in direct comparison study. For these reasons, downgrade from Moderate to Low.

# Conclusions

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## Single-Test Studies

Limited direct/indirect evidence that iFOBT has superior sensitivity/specificity to unrehydrated gFOBT for CRC detection:

- Sensitivity for gFOBT 13% and 25% (see bottom of page 18 for details)
- Pooled iFOBT sensitivity 81%

Compared to their ability to detect CRC, iFOBT and gFOBT have lower sensitivity for adenoma detection:

- Sensitivity for rehydrated gFOBT 22%
- Pooled iFOBT sensitivity 28%

## Repeated-Test Studies

No trials examined CRC mortality outcomes after repeated testing of iFOBT.

RCTs showed significant reduction in CRC mortality using unrehydrated gFOBT biennially:

- RR reductions of 13% (UK trial) and 16% (Danish trial); absolute difference of 0.1% (UK trial) and 0.2% (Danish trial)
- No significant reduction in overall mortality

Interval cancers (CRC that develops in the intervals between routine screening)

- United Kingdom trial had 236 CRCs that were detected by a positive test and 236 interval CRCs that were detected after a negative test
- Danish trial had 120 CRCs that were detected by a positive test and 146 interval CRCs that were detected after a negative test

Unrehydrated gFOBT has low sensitivity for CRC detection (45% and 54%).

- True positive rate 50% (United Kingdom and Danish RCTs)
- False positive rate 5%–10%
- True negative rate 90%–95% (from observational studies, because RCTs did not report specificity)
- False negative rate 50%

## Existing Guidelines

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In May 2008, the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology jointly issued guidelines for the detection of adenomatous polyps and CRC in asymptomatic, average-risk adults. It grouped screening tests into those that primarily detect cancer and those that can detect cancer and adenomatous polyps, thereby increasing the potential for CRC prevention through polypectomy. (2)

When possible, clinicians should make patients aware of the full range of screening options but at a minimum they should be prepared to offer a choice between a screening test that's primarily effective at early cancer detection and a screening test that's effective at both early cancer detection and cancer prevention through the detection and removal of polyps. It is the strong opinion of these three organizations that colon cancer prevention should be the primary goal of screening. Table 10 shows examples of tests in each category.

**Table 10: Testing Options for the Early Detection of CRC and Adenomatous Polyps**

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**Tests That Detect Adenomatous Polyps and Cancer**

- flexible sigmoidoscopy every 5 years, or
- colonoscopy every 10 years, or
- double contrast barium enema every 5 years, or
- CT colonography every 5 years

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**Tests That Primarily Detect Cancer**

- annual gFOBT with high test sensitivity for cancer, or
  - annual iFOBT with high test sensitivity for cancer, or
  - stool DNA with high sensitivity for cancer, interval uncertain
- 

From: Joint Guideline from the American Cancer Society, US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (2)

The panel recognized that some people will not want to undergo an invasive test that requires bowel preparation, may prefer to be screened in the privacy of their homes, or may not have access to more invasive tests due to the limits of local resources. (2) The panel commented that patients and physicians should understand the following limitations and requirements of noninvasive tests: (2)

- They are less likely to prevent cancer compared with invasive tests.
- They must be repeated at regular intervals to be effective.
- If the result is abnormal, an invasive test (colonoscopy) is required.

# Ontario Health System Impact Analysis

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## Considerations and/or Implications

### Diffusion: International

Organized CRC screening pilot programs using FOBT have been implemented in some jurisdictions (e.g. United Kingdom, Australia, Finland). (28)

#### *United Kingdom*

1. English Bowel Cancer Screening Pilot
  - The objective was to assess the feasibility of introducing a national CRC screening program using FOBT.
  - The pilot ended in March 2007.
  - Participants were age 50–69 years.
  - 478,250 people were invited to take part in the pilot. Update (the proportion in whom a final FOBT result was available) was 56.8% (271,646).
  - The overall rate of a positive test result was 1.9%.
  - Positive predictive value was 10.9% for cancer and 35.0% for adenoma.
2. NHS Bowel Cancer Screening Program
  - A national screening program using FOBT began in England in July 2006 and with nationwide coverage by 2009.

#### *Australia*

1. Australia Bowel Cancer Screening Pilot (29)
  - A pilot study aimed at assessing the feasibility, acceptability and cost effectiveness of iFOBT in people aged 55 to 74 in both urban and rural settings. It ran between November 2002 and June 2004. The proposed interval for iFOBT screening was biennial; however, only one round of screening took place during the pilot.
  - A total of 56,907 people were invited to participate in the pilot, which had a participation rate of 45.5%.
  - Of the 25,688 correctly completed iFOBTs that were analyzed, 2,317 (9.0%) were positive and 23,371 (91.0%) were negative.
  - The positive predictive value for suspected cancers and advanced adenomas across both tests was 19.2%.
  - There were 1,833 follow-up colonoscopies recorded for the pilot, some of which related to participants without a positive iFOBT. These colonoscopies identified 69 cancers and 195 advanced adenomas, including those detected in pilot participants who did not have a positive FOBT result.
  - Pilot sites reported a substantial increase in staff workload, in part due to a significantly higher FOBT positivity rate than was originally anticipated.
  - There was significant loss to follow-up with incomplete records for many pilot participants. For many with a positive FOBT, the register held no record of follow-up colonoscopy.
  - Workforce capacity to meet increases in demand depends on the FOBT positivity rate and workforce modeling will need to be undertaken to further assess potential impacts of the program.

## 2. National Bowel Cancer Screening Program Implementation (30)

- The National Bowel Cancer Screening Program was to be phased in over a number of years, beginning in August 2006. Initially, screening was offered to Australians 55 or 65 years of age between May 2006 and June 2008, and those who were involved in the Pilot Program, which ran from November 2002 to June 2004. The program was being phased in gradually to help ensure that health services such as colonoscopy and treatment services were able to meet any increased demand.
- People eligible to participate were to receive an invitation through the mail to complete an iFOBT and mail it to a laboratory.
- An evaluation of this phase of the National Bowel Cancer Screening Program was to be completed in 2007–2008.

### *Finland*

- The CRC screening program was launched in September 2004. (31) The target group of the program is senior citizens between the ages of 60 and 69. Screening is being gradually expanded to cover this whole age group. Initially it has focused on 60, 62 and 64-year-olds.
- Of the 440 Finnish municipalities, 120 were in the program in 2005. More than 30 municipalities joined the program in 2006.

### **Diffusion: National**

#### *Ontario*

In January 2007, Cancer Care Ontario and the Ministry of Health and Long-Term Care jointly announced a population-based CRC screening program for Ontario. The program uses FOBT for screening those at average risk and colonoscopy as the initial screening test for those at increased risk because of a history of one or more first-degree relatives diagnosed with CRC. Colonoscopy is used to investigate the approximately 2%–3% of screenees who have a positive FOBT. (1)

#### *Quebec*

The Quebec Association of Gastroenterology released a position paper on CRC in 2003. (32) Based on the evidence from outcome studies and diagnostic test characteristics of the different screening tools, the committee recommended that a screening program should be based on the performance of 5- to 10-yearly DCBE or 10-yearly colonoscopy without waiting for high-quality evidence for their use. (32) They also recommended that “an effort should also be made to monitor patients undergoing what may be less effective methods of screening (such as FOBT and/or flexible sigmoidoscopy).” (32)

### **System Pressures**

Table 11 summarizes potential system pressures and a benefit/risk analysis of using FOBT and colonoscopy to screen for CRC in average-risk adults at least 50 years of age in Ontario.

**Table 11: Potential System Pressures and Benefit/Risks of FOBT and Colonoscopy for CRC Screening**

Criteria	Colonoscopy*	FOBT*
Primarily prevent or detect cancer?	<ul style="list-style-type: none"> <li>Prevent and detect</li> </ul>	<ul style="list-style-type: none"> <li>Detect</li> </ul>
Frequency of screening	<ul style="list-style-type: none"> <li>Every 10 years</li> <li>Must repeat at regular intervals</li> </ul>	<ul style="list-style-type: none"> <li>Every 2 years</li> <li>Must repeat at regular intervals</li> </ul>
Level of evidence	<ul style="list-style-type: none"> <li>Observational</li> </ul>	<ul style="list-style-type: none"> <li>RCTs</li> </ul>
Benefit	<ul style="list-style-type: none"> <li>Used as gold standard in studies</li> </ul>	<ul style="list-style-type: none"> <li>Intervention GRADE quality for gFOBT High</li> <li>Diagnostic GRADE quality for iFOBT Low (No RCTs examining the effectiveness of repeated iFOBT on CRC mortality reduction were identified)</li> <li>Limited direct/indirect evidence that iFOBT has superior sensitivity/specificity to unhydrated gFOBT for detection of CRC</li> </ul>
Risk	<ul style="list-style-type: none"> <li>0.1% risk of serious bleeding and perforation requiring surgery</li> <li>0.3% risk of serious complications (stroke/bleeding requiring hospitalization/ myocardial infarction)</li> </ul>	<ul style="list-style-type: none"> <li>High interval cancer rate.</li> <li>The small benefit in CRC mortality reduction (absolute difference 0.1% to 0.2%) also coincides with a 0.3% risk of serious complications.</li> </ul>
Need for preparation	<ul style="list-style-type: none"> <li>No food 1 day prior to exam</li> <li>Office/hospital visit</li> <li>Complete bowel preparation</li> <li>Sedation</li> </ul>	<ul style="list-style-type: none"> <li>Eliminate citrus fruit and juices and vitamin C from diet 3 days prior to/during stool collection</li> <li>Person applies 2 samples per bowel movement (each occurring on 3 different days) onto test areas of FOBT cards</li> </ul>
Resources required for screening asymptomatic, average-risk adults ≥ 50 years	<ul style="list-style-type: none"> <li>Increased demand for colonoscopies and colonoscopists or nurses who perform colonoscopies</li> </ul>	<ul style="list-style-type: none"> <li>Patient receives kit from family physician, pharmacist</li> <li>Patients mail completed FOBT kit to participating laboratory</li> <li>Results sent back to patient</li> <li>Increased demand for colonoscopies for (positive) patients</li> </ul>
Screening test (positive)	<ul style="list-style-type: none"> <li>Removal of polyp during colonoscopy or surgery</li> </ul>	<ul style="list-style-type: none"> <li>Referral to colonoscopy</li> </ul>
Cost-effectiveness	<ul style="list-style-type: none"> <li>Cost-effective</li> </ul>	<ul style="list-style-type: none"> <li>Cost-effective</li> </ul>
Patient preference	<ul style="list-style-type: none"> <li>2nd out of 5 choices in a patient survey study (27)</li> </ul>	<ul style="list-style-type: none"> <li>5th out of 5 choices in a patient survey study (27)</li> </ul>

CRC indicates colorectal cancer; FOBT, fecal occult blood test; gFOBT, guaiac FOBT; GRADE, Grading of Recommendations Assessment, Development and Evaluation; iFOBT, immunochemical FOBT; RCT, randomized controlled trial.

\*Screening average-risk adults, aged 50 and over



Glossary

**Adenoma:** a benign epithelial tumor in which the cells form recognizable glandular structures or in which the cells are clearly derived from glandular epithelium.

**Diagnostic case control study:** a study in which the index test results for a group of patients already known to have the disease (through the reference standard) are compared with the index test results with a separate group of normal/healthy people known to be free of the disease (through the use of a reference standard).

**Diagnostic cohort study:** a study in which patients are selected and the experimental test and reference standard are applied to all patients satisfying the entrance requirements.

**Negative predictive value:** the proportion of people with a negative test who are free of the target disorder.

**Neoplasm:** any new and abnormal growth; specifically a new growth of tissue in which the growth is uncontrolled and progressive.

**Polyp:** a morbid excrescence, or protruding growth, from a mucous membrane.

**Positive predictive value:** the proportion of people with a positive test who have the target disorder.

# Appendices

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## Appendix 1: Search Strategy

Search date: June 20, 2008

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations; EMBASE, Cochrane Library, International Agency for Health Technology Assessment/Centre for Reviews and Dissemination (INAHTA/CRD)

Database: Ovid MEDLINE(R) <1996 to June Week 2 2008>

### Search Strategy:

- 1 exp Colorectal Neoplasms/ (54483)
- 2 exp Intestinal Polyps/ (3177)
- 3 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (65836)
- 4 exp Precancerous Conditions/ (10855)
- 5 or/1-4 (78248)
- 6 exp Occult Blood/ (1509)
- 7 (f?ecal occult blood test\$ or fobt\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1041)
- 8 ((f?ecal or f?eces) adj2 (blood or immunochemical or guaiac)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1581)
- 9 exp Guaiac/ (57)
- 10 (hemoccult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or Insure or flexsure\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (310)
- 11 or/6-10 (2387)
- 12 5 and 11 (1508)
- 13 limit 12 to (humans and english language and yr="2003 - 2008") (679)
- 14 limit 13 to (controlled clinical trial or meta analysis or randomized controlled trial) (56)
- 15 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (32618)
- 16 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (61753)
- 17 exp Random Allocation/ or random\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (356301)
- 18 exp Double-Blind Method/ (51508)
- 19 exp Control Groups/ (593)
- 20 exp Placebos/ (8940)
- 21 RCT.mp. (2353)
- 22 or/14-21 (427538)
- 23 13 and 22 (140)

Database: EMBASE <1980 to 2008 Week 24>

### Search Strategy:

- 1 exp Large Intestine Tumor/ (99648)
- 2 exp Colorectal Tumor/ (1950)
- 3 exp Intestine Polyp/ (10325)
- 4 exp PRECANCER/ (6051)
- 5 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (106881)
- 6 or/1-5 (127732)

7 exp Occult Blood Test/ or exp Occult Blood/ (3727)  
8 (f?ecal occult blood test\$ or fobt\$).mp. [mp=title, abstract, subject headings, heading word, drug trade  
name, original title, device manufacturer, drug manufacturer name] (1365)  
9 ((f?ecal or f?eces) adj2 (blood or immunochemical or guaiac)).mp. [mp=title, abstract, subject headings,  
heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2475)  
10 exp GUAIAC/ (131)  
11 (hemoccult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or  
!nsure or flexsure\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title,  
device manufacturer, drug manufacturer name] (742)  
12 or/7-11 (4957)  
13 6 and 12 (2786)  
14 limit 13 to (human and english language and yr="2003 - 2008") (941)  
15 Randomized Controlled Trial/ (158484)  
16 exp Randomization/ (25640)  
17 exp RANDOM SAMPLE/ (1129)  
18 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (285860)  
19 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$) or published studies or  
published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (58693)  
20 Double Blind Procedure/ (69461)  
21 exp Triple Blind Procedure/ (10)  
22 exp Control Group/ (1831)  
23 exp PLACEBO/ (114035)  
24 (random\$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title,  
device manufacturer, drug manufacturer name] (410302)  
25 or/15-24 (624810)  
26 14 and 25 (203)

## Appendix 2: Overall Conclusions of Systematic Reviews

**Table A1: Overall Conclusions of Systematic Reviews Identified in the Literature Search**

Publication Date (Literature Search Cut-off Date)	Country	Organization	Overall Conclusion
Jan 2008  (Dec 2006)	Canada	Screening Action Group of the Canadian Partnership Against Cancer	<ul style="list-style-type: none"> <li>▪ Due to heterogeneity, it was not possible to pool information to determine which FOBT to use in CRC screening programs.</li> <li>▪ iFOBT appeared to have a greater sensitivity for cancer detection. Choice of a specific FOBT for a screening program requires balancing sensitivity with other indicators such as PPV and FOBT positive rate.</li> <li>▪ PPV and FOBT positive rates varied widely for gFOBT and iFOBT and appeared to be dependent on study design and demographics of the study participants. Choice of a specific FOBT needs to be balanced with the chosen design for the CRC screening program and the demographics of the screening population.</li> </ul>
Jan 2008  (Feb 2006)	United Kingdom	Cochrane Collaboration	<ul style="list-style-type: none"> <li>▪ Combined results from 4 RCTs show a 16% reduction in the RR of CRC mortality (RR, 0.84; 95% CI, 0.78–0.90). In the 3 studies that used biennial screening (Funen, Minnesota, Nottingham) there was a 15% RR reduction in CRC mortality (RR, 0.85; 95% CI, 0.78–0.92).</li> <li>▪ When adjusted for screening attendance in individual studies, there was a 25% reduction in RR (RR, 0.75; 95% CI, 0.66–0.84) for those attending at least one round of screening using FOBT. This review found that FOBT screening is likely to avoid approximately 1 in 6 CRC deaths.</li> </ul>
Dec 2007  (Nov 2004)	New Zealand	New Zealand Health Technology Assessment	<ul style="list-style-type: none"> <li>▪ High-quality evidence that FOBT screening with gFOBT (Hemoccult) reduces mortality from CRC. Specifically, evidence from ongoing follow-up for 3 major RCTs suggests that this reduction is sustainable for the populations in which screening has stopped, but the reduction decreased in magnitude slightly for the population to whom screening has continued to be offered.</li> <li>▪ While less robust, the direct evidence available suggests that a reduction in rectal cancer may be achievable with the use of an immunochemical test.</li> <li>▪ Limited definitive evidence regarding superiority of iFOBT over gFOBT; however, evidence from cross-sectional studies suggests that iFOBT (HemeSelect) is comparable to or superior to gFOBT.</li> <li>▪ Simplified FOBT tests may be more acceptable as there was good evidence that the simplified testing process and sampling kit of iFOBT (Insure) encouraged greater participation rates.</li> </ul>
Aug 2007  (Mar 2007)	United Kingdom	Centre for Reviews and Dissemination, University of York	<ul style="list-style-type: none"> <li>▪ Studies that included direct comparisons indicated a better overall test performance of iFOBT than for gFOBT, but this evidence was very limited and of poor quality. Indirect comparisons showed no clear evidence to suggest that either gFOBT or iFOBT performed better.</li> <li>▪ Poor data reporting limited the scope of the review. The authors encouraged investigators to use the Standards for the Reporting of Diagnostic accuracy studies (STARD) guidelines when reporting diagnostic accuracy studies.</li> <li>▪ Less reliable indirect comparisons failed to identify a clear preference for either gFOBT or iFOBTs.</li> <li>▪ Other than accuracy, factors to be considered when deciding which FOBT to use include the effects of sampling methods, dietary restrictions, sample storage and transportation issues, and cost-effectiveness. Data included in the review provided no clear evidence on any of these factors.</li> </ul>

Dec 2006  (Oct 2006)	Belgium	Federaal Kenniscentrum voor de Gezondheidszorg (KCE)	<ul style="list-style-type: none"> <li>▪ Effectiveness of mass screening has been investigated in average-risk males and females starting from the age of 45 or 50 and up to the age of 75 years. Only for the gFOBT is there high-quality evidence that screening reduces CRC mortality. The estimated reduction attributable to screening is around 15% in RCTs in intention-to-screen analyses and around 33% in per-protocol analyses. Although there is high-quality evidence that FOBT-based screening can reduce CRC mortality, there is no evidence for overall mortality reduction.</li> <li>▪ The study recommended implementation of a few pilot screening programs to investigate some key issues that need to be addressed and resolved: participation rates, compliance and acceptance of the screening program in Belgium, prevalence of increased CRC risk, positivity rates and sensitivity/specificity of FOBT in real-world circumstances, CRC and adenoma detection rates by colonoscopy after positive FOBT and harms caused by the screening program, performance of iFOBT compared with gFOBT.</li> </ul>
May 2004  (Feb 2004)	Australia	Medical Services Advisory Committee (MSAC)	<ul style="list-style-type: none"> <li>▪ Safety</li> <li>▪ The head-to-head studies identified in this assessment of the relative screening performance of different FOBTs in an average-risk population did not report any safety data. Therefore, the performance of the various FOBTs for population health screening cannot be assessed on the basis of safety data.</li> <li>▪ Effectiveness</li> <li>▪ Three head-to-head studies estimated the sensitivity and specificity of various FOBTs using the interval cancer rate. Two more studies reported data that enabled calculation of the relative true positive rate (TPR) and the relative false positive rate (FPR) of the FOBTs compared. There were no studies of a suitable quality available to allow assessment of the relative accuracy of the different FOBTs for the detection of adenomas.</li> <li>▪ HemeSelect was found to be significantly more sensitive than Hemoccult, whereas the Hemoccult test was significantly more specific than HemeSelect. There was no significant difference in sensitivity between Hemoccult and Fecatwin Sensitive/Feca; however, Hemoccult was significantly more specific than Fecatwin Sensitive/Feca EIA. There was no significant difference in sensitivity between Hemoccult Sensa and HemeSelect, but HemeSelect proved to be significantly more specific than Hemoccult Sensa.</li> <li>▪ Summary of outcomes</li> <li>▪ The MSAC considers that FOBT is useful for population health screening to reduce CRC mortality. The available evidence indicates that there is no apparent class effect for the guaiac versus immunochemical FOBTs with regard to their effectiveness or cost-effectiveness. Different brands of FOBTs possess different sensitivities and specificities for the detection of CRC within an average-risk screening population.</li> </ul>

CRC indicates colorectal cancer; RR, relative risk

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