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Evidence-Based Series 15-8 EDUCATION AND INFORMATION 2016

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
and the ColonCancerCheck Clinical Advisory Committee, CCO

Fecal Immunochemical Tests Compared With Guaiac Fecal Occult Blood Tests for Population-Based Colorectal Cancer Screening

L. Rabeneck, R.B. Rumble, F. Thompson, M. Mills, C. Oleschuk, A.H. Whibley, H. Messersmith, and N. Lewis: The FIT Guidelines Expert Panel

Report Date: November 8, 2011

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The full Evidence-based Series (EBS) 15-8 is comprised of 3 sections

Section 1: Recommendations
Section 2: Evidentiary Base
Section 3: Methodology of the Recommendations Development and External Review Process

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Journal Citation (Vancouver Style): Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol. 2012 Mar;26(3):131-47.

Guideline Citation (Vancouver Style): Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley AH, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Toronto (ON): Cancer Care Ontario; 2011 Nov 8 [Ed & Info 2016 April]. Program in Evidence-based Care Evidence-based Series No.: 15-8 Education and Information 2016.

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Evidence-Based Series 15-8: Section 1

Fecal Immunochemical Tests Compared With Guaiac Fecal Occult Blood Tests for Population-Based Colorectal Cancer Screening: Guideline Recommendations

L. Rabeneck, R.B. Rumble, F. Thompson, M. Mills, C. Oleschuk, A.H. Whibley, H. Messersmith, and N. Lewis: The FIT Guidelines Expert Panel

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Report Date: November 8, 2011

GUIDELINE OBJECTIVE

The purpose of this guideline is to evaluate the existing evidence concerning fecal immunochemical test (FIT) to inform the decision on how to replace the current guaiac fecal occult blood test (gFOBT) with a FIT in Ontario's ColonCancerCheck Program.

To address this guideline objective, the following three clinical issues were considered:

1. **FIT Performance Factors**
   What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value [PPV]) of FIT when used to detect colorectal cancer (CRC)?

2. **FIT Kit Usability Factors**
   What FIT kit factors affect acceptability by users (e.g., card versus vial collection FIT, medication use)?

3. **Specimen Stability**
   What factors affect specimen stability?

INTENDED USERS

Primary care providers, other health care practitioners, and policy makers responsible for the design and implementation of colorectal cancer screening programs.

FINDINGS

The findings of the investigation of the three clinical issues were as follows.

FIT Performance Factors
Sensitivity In one study (1), FIT demonstrated greater sensitivity for detecting both CRC ($p<0.01$) and advanced adenoma (AA) ($p<0.05$) compared with gFOBT.
Detection of Advanced Neoplasia (combined outcome of CRC and AA) Two studies reported greater detection of advanced neoplasia with FIT compared with gFOBT (2,3).
Specificity One study that used a high-sensitivity gFOBT found significantly greater specificity associated with FIT (4) for detecting both CRC and AA, and two studies that used a standard gFOBT found significantly greater specificity with gFOBT (2,3); one for both CRC and AA (3), and one for AA only (2).
Positivity Two of the studies obtained reported significantly higher positivity rates associated with FIT (2,3) compared with standard gFOBT, and the study that used a high-sensitivity gFOBT reported significantly higher positivity rates associated with gFOBT (4).
PPV Studies that used a standard gFOBT found no significant difference in PPV for the detection of CRC and AA for FIT compared with gFOBT. One of the studies obtained that used a high sensitivity gFOBT found significantly higher PPV associated with FIT for detecting both CRC and AA (4). For FITs that produce a numerical result, these performance characteristics can vary, depending on the cut-off level in hemoglobin concentration used to define a positive FIT.
FIT Kit Usability Factors
Three randomized controlled trials (RCTs) (2,3,5) found superior screening participation rates with FIT compared with gFOBT (all $p<0.05$).
Specimen Stability
Two studies reported on specimen stability using FIT with respect to temperature and time (6,7) and found that higher temperatures (e.g., summer versus winter) and longer times between stool sampling and laboratory processing are associated with lower positivity rates.
Qualifying Statement
The use of FIT is associated with greater specimen instability for both time between stool sampling and kit processing (according to the manufacturer's inserts, only three of the examined FITs are stable for ≥ 7 days, and only two are stable for ≥ 15 days) and temperature (two studies [(6,7)] reported an association between lower temperatures and longer stability). FIT may also be associated with higher positivity rates than is standard gFOBT. Three studies found higher positivity rates associated with FIT (1-3), two of which were statistically significantly higher (2,3), while only one of the studies found significantly higher positivity rates associated with gFOBT (4), in a comparison between the FIT and a high sensitivity gFOBT. Therefore, any screening program considering the use of FIT needs to take these factors into account.

RECOMMENDATIONS

The FIT Guidelines Expert Panel recommends that a pilot study be performed to investigate how to implement FIT in the population-based CRC screening program in Ontario. This pilot study should evaluate FIT based on laboratory, field, and economic factors. The laboratory component would evaluate specimen stability under varying conditions and the feasibility of automation. The field component would evaluate kit distribution, labelling of kits, stool sampling, and transportation of completed kits to the laboratory. An economic evaluation would be included.

Evidence

Eleven papers were included in this guideline, comprising two systematic reviews (8,9), five papers reporting on three RCTs (2,3,5,10,11), and reports of four other studies (1,4,6,12). Additionally, a laboratory study by Lamph et al (7) was obtained that reported on several parameters of FITs that helped to inform this recommendation. The performance of FIT is superior to the standard gFOBT in terms of screening participation rates and the detection of CRC and AA. Given greater specimen instability with the use of FIT, a pilot study should be undertaken to determine how to implement the FIT in Ontario.

Any program implemented should use automated kit labelling (e.g., bar code) and not require a separate requisition for the kit.

Evidence

This recommendation is supported by findings from the current ColonCancerCheck program.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario. It is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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Evidence-Based Series 15-8: Section 2

Fecal Immunochemical Tests Compared With Guaiac Fecal Occult Blood Tests for Population-Based Colorectal Cancer Screening: Evidentiary Base

L. Rabeneck, R.B. Rumble, F. Thompson, M. Mills, C. Oleschuk, A.H. Whibley, H. Messersmith, and N. Lewis: The FIT Guidelines Expert Panel (see Appendix A).

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
and the ColonCancerCheck Clinical Advisory Committee, CCO

Report Date: November 8, 2011

GUIDELINE OBJECTIVE

The purpose of this guideline is to evaluate the existing evidence concerning fecal immunochemical test (FIT) to inform the decision on how to replace the current guaiac fecal occult blood test (gFOBT) with a FIT in Ontario's ColonCancerCheck Program.

To address this guideline objective, the following three clinical issues were considered:

1. **FIT Performance Factors**
   What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value [PPV]) of FIT when used to detect colorectal cancer (CRC)?

2. **FIT Kit Usability Factors**
   What FIT kit factors affect acceptability by users (e.g., card versus vial collection FIT, medication use)?

3. **Specimen Stability**
   What factors affect specimen stability?

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer deaths in Canadian men and women, accounting for almost 12% of all cancer deaths (1). In Ontario in 2011, it is estimated that 8,100 persons will be diagnosed with CRC, and 3,250 will die from the disease (1). Colorectal cancer incidence and mortality rates in Ontario are among the highest in the world (2). Screening offers the best opportunity to reduce this burden of disease.

The two CRC screening methods recommended by the Canadian Task Force on Preventive Health Care for men and women at average risk for CRC (i.e., asymptomatic, 50 years of age and older, and with no other risk factors for CRC) are the fecal occult blood test (FOBT) and flexible sigmoidoscopy (FS) (3). These recommendations are supported by evidence from randomized controlled trials (RCTs). In the 1990s, evidence from RCTs demonstrated that screening with the FOBT (coupled with colonoscopy for those who test positive) is associated with a decrease in CRC mortality and an increase in the proportion of detected cancers that are Dukes' Stage A (4-6). In 2010, results from the United Kingdom (UK) Flexible Sigmoidoscopy trial also demonstrated that screening with flexible sigmoidoscopy (FS) is associated with a decrease in CRC mortality (7).

In January 2007, the Ontario Ministry of Health and Long-Term Care announced funding for a province-wide, population-based CRC screening program. The program, ColonCancerCheck, uses FOBT for screening those at average risk and colonoscopy as the initial screening test for those at increased risk because of a family history of one or more first-degree relatives diagnosed with CRC. Colonoscopy is also used to investigate screenees who have a positive FOBT. Colonoscopy Standards were developed by CCO's Program in Evidence-Based Care (PEBC) to support the ColonCancerCheck Program (8).

Prior to the launch of ColonCancerCheck, an Expert Panel was convened by the PEBC to evaluate the evidence concerning existing guaiac FOBT (gFOBT) kits and, based on this evidence, to develop gFOBT Standards for the Ontario CRC Screening Program (9). The standards provided a basis for selecting the gFOBT kit used by the ColonCancerCheck Program and determined the laboratory requirements for the Program. The selected gFOBT kit has been in use since April 2008.

At the time the gFOBT Laboratory Standards Expert Panel began its work in the fall of 2006, the fecal immunochemical test (FIT) was undergoing evaluation in various settings. However, the body of evidence was not large, and FIT was not endorsed for CRC screening by a screening guideline from any jurisdiction. However, the Expert Panel anticipated the need to evaluate the evidence concerning FIT, as the body of evidence developed.

This FIT Guidelines Expert Panel was convened in September 2010 by the PEBC to evaluate the evidence concerning existing FIT kits and, based on this evidence, to set forth FIT Guidelines for the ColonCancerCheck Program.

The gFOBT and the FIT are different. GFOBT detects blood in the stool which may be due to bleeding from CRC. To complete a gFOBT, participants are required to apply six fecal samples (two samples from each of three consecutive spontaneously passed stools) onto test areas (windows) on FOBT cards, a type of sampling referred to as a "dry" method in the literature. The test is based on the oxidation of guaiac (impregnated on the card) by hydrogen peroxide catalyzed by the peroxidase activity of hemoglobin. The disadvantage of this reaction is that it will occur with any peroxidase found in the feces (e.g., plant peroxidases, heme in red meat) and is affected by certain chemicals (e.g., vitamin C) (10). Thus, gFOBTs are not specific for human hemoglobin. gFOBTs may also detect bleeding from any site in the gastrointestinal tract, including the stomach (11). The gFOBT is visually read by trained laboratory technicians using the "naked eye" to interpret a visual result.

In contrast, FIT uses an antibody against human globin, the protein part of hemoglobin. FIT is specific for human hemoglobin, and is more specific than the gFOBT for bleeding from the distal gut (i.e., colon and rectum). To complete a FIT, participants sample one or more stools using various sampling systems, and samples are either applied to a card (dry method) or placed into a vial, a type of sampling referred to in the literature as a wet method. Devices used to collect the stool include wooden sticks and brushes. For some manufacturer's FIT kits, samples are analyzed using automated systems in the laboratory. These systems provide a numerical result and allow for a customized cut-off in hemoglobin

concentration to be set to define a positive test. In contrast, other FIT kits are designed as point-of-care devices with pre-specified cut-off points used to define a positive result. Similar to gFOBT, they are read by the naked eye with a positive result indicated by a colour change on a strip. They are designed for doctor's offices or clinics, but can be adapted for use in clinical laboratories for high volume population-based screening, albeit using a more manual approach compared with the automated systems.

Although there are many brands of FIT kits available, the focus of this document is on the 13 FITs that are currently approved in Canada for processing in a laboratory setting (Level 2 approval, Health Canada) (see Table 1). The Expert Panel opinion is that test processing in laboratories rather than point-of-care processing is essential for a population-based screening program, which requires quality control protocols in laboratories as well as population-level data collection to monitor program performance.

Table 1. FITs with an active license approved for use by Health Canada. (See Appendix B for complete details from the manufacturers' inserts and/or provided literature.)

Manufacturer / Distributor	Device	Product description	Numeric or visual result
Eiken / Polymedco	OC-Auto Micro 80 FOB Test System (believed equivalent to OC-Hemodia)	Flat tube, dipstick collection, machine developed	Numeric
Eiken / Polymedco	OC-Sensor DIANA IFOB Test System (Assumed the same as OC-Auto Micro)	Flat tube, dipstick collection, machine developed	Numeric
Alfresa Pharma Corp / Inverness Medical	I-FOBT Hemoglobin NS-Plus	Flat tube, dipstick collection, machine developed	Numeric
Beckman Coulter	Hemoccult ICT, Immunochemical Fecal Occult Blood Test (A.K.A. Flexsure OBT)	Test card, applicator stick, on card developed	Visual
Eiken / Polymedco	OC-Light Manual IFOBT	Long cylindrical tube, dipstick collection, test strip developed	Visual
Inverness Medical	Clearview Ultra FOB Test	Long cylindrical tube, dipstick collection, test strip developed	Visual
Medix Biochemica	Actim Fecal Blood Test	Cylindrical tube, sampling stick that then is put into the tube, development occurs on the stick	Visual
PSS World Medical	Consult Diagnostic Occult Blood Test Extra Sensitive	Unknown	Insert/instructions not available
Artron	One Step Fecal Occult Blood Test	Cylindrical tube, dipstick sampling, developed on a cassette	Visual
IND Diagnostic / BTNX	Rapid Response One-Step Fecal Occult Blood Test	Cylindrical tube, dipstick sampling, developed on a cassette	Visual
Tremblay-Harrison	Minute Lab Fecal Occult Blood Test Device	Cylindrical tube, dipstick sampling, developed on a cassette	Visual

Manufacturer / Distributor	Device	Product description	Numeric or visual result
WHPM Bioresearch & Technology	Hemosure Immunological Fecal Occult Blood Test	Cylindrical tube, dipstick sampling, developed on a cassette	Visual
Innovacon	FOB One Step Fecal Occult Blood Test	Cylindrical tube, dipstick sampling, developed on a cassette	Visual

METHODS

Clinical Questions

To inform recommendations regarding how to replace the current gFOBT with a FIT in the population-based CRC screening program in Ontario, the Expert Panel set out to evaluate existing evidence concerning the following three key aspects of FIT kit use:

1. **FIT Performance Factors**
   What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value [PPV]) of FIT when used to detect colorectal cancer (CRC)? (see Appendix C for definitions of the diagnostic parameters)

2. **FIT Kit Usability Factors**
   What FIT kit factors affect acceptability by users (e.g., card or "dry" versus vial or "wet" collection FIT, medication use)?

3. **Specimen Stability**
   What factors affect specimen stability?

Literature Search

The MEDLINE and EMBASE databases were systematically searched for articles assessing FIT screening for CRC published between 1996 and indexed through June 2010. The search strategies used are listed in Appendix D. Additionally, the websites of a large number of agencies and organizations were also searched for evidence, and a listing of all sources searched and the number of articles ordered and retained appears in Table 2. Expert Panel members were also canvassed to ensure that no relevant articles were missed.

In addition to the evidence obtained in this review, the knowledge obtained from the ColonCancerCheck Program will be considered when making recommendations.

Table 2. Literature search sources.

Source/database	Date searched	Number of hits	Ordered for full-text review	Retained
Systematic search. See Appendix D for strategies used.				
MEDLINE	June 17, 2010	227	33	4
EMBASE	June 17, 2010	362	31	0*
Keyword search. Terms used: fecal occult blood test, immunochemical, FIT, FOBT, colorectal cancer, screening				
Canadian organizations				
BC Cancer Agency (www.bccancer.bc.ca)	Oct 12, 2010	0	-	-
Alberta Cancer Board	Oct 12, 2010	0	-	-

Source/database	Date searched	Number of hits	Ordered for full-text review	Retained
(www.cancerboard.ab.ca)				
Saskatchewan Cancer Agency (www.saskcancer.ca)	Oct 12, 2010	0	-	-
Cancer Care Manitoba (www.cancercare.mb.ca)	Oct 12, 2010	0	-	-
Cancer Care Nova Scotia (www.cancercare.ns.ca)	Oct 12, 2010	0	-	-
U.S. organizations				
NGC (www.guidelines.gov)	June 17, 2010	5		
AHRQ HTA (www.ahrq.gov)	Oct 12, 2010	1	0	-
ASCO (www.asco.org)	Oct 12, 2010	0	-	-
NCCN (www.nccn.org)	Oct 12, 2010	1	0	-
U.K. organizations				
Cochrane database of Systematic Reviews	June 17, 2010	1	1	1
UK NHS HTA (www.hta.ac.uk)	Oct 12, 2010	0	-	-
NICE (www.nice.org.uk)	Oct 12, 2010	2	2**	-
SIGN (www.sign.ac.uk)	Oct 12, 2010	0	-	-
Cancer UK (www.canceruk.org)	Oct 12, 2010	0	-	-
Cancer Services Collaborative, Avon, Somerset, and Wiltshire (www.aswcs.nhs.uk)	Oct 12, 2010	0	-	-
NHS (www.nhs.uk)	Oct 12, 2010	6	0	-
Australian organizations				
National Health & Medical Research Council (www.nhmrc.gov.au)	Oct 12, 2010	1	0	-
The Cancer Council Australia (www.cancer.org.au)	Oct 12, 2010	1	0	-
National Cancer Control Initiative (www.canceraustralia.gov.au)	Oct 12, 2010	0	-	-
State Government of Victoria (www.vic.gov.au)	Oct 12, 2010	0	-	-
Peter MacCallum Cancer Centre (www.petermac.org)	Oct 12, 2010	0	-	-
Medical Oncology Group of Australia (www.moga.org.au)	Oct 12, 2010	0	-	-
New Zealand organizations				
New Zealand Guidelines Group (www.nzgg.org.nz)	Oct 12, 2010	1	0	-
NZ Cancer Control Trust (wwwcancercontrol.org.nz)	Oct 12, 2010	0	-	-
Obtained through other resources (e.g. papers forwarded by panel members, etc.)				
Various	various	NA	NA	6
			TOTAL	**11**

*no EMBASE articles remained after MEDLINE duplicates were removed.
** duplicate publications found in MEDLINE search.
Note: FIT, fecal immunochemical test; FOBT, fecal occult blood test; BC, British Columbia; U.S., United States; NGC, National Guidelines Clearinghouse; AHRQ, Agency for Healthcare Research & Quality; HTA, Health Technology Assessment; ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; U.K./UK, United Kingdom; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; SIGN, Scottish Intercollegiate Guidelines Network.

Selection Criteria

Eligible sources of information had to meet the following criteria:

1. Published full reports with information on any of performance, usability, or specimen stability factors as listed above.
2. Systematic reviews (SRs), randomized controlled trials (RCTs), other prospective study designs, retrospective study designs, and mixed design studies. For the purpose of this paper, systematic reviews including those that are the evidentiary foundation for clinical practice guidelines or health technology assessments, or similar reports were included, provided that they reported in detail (e.g., search methods, selection criteria) on a systematic search and summary of the health care literature for articles on a relevant topic.
3. Reports published in English.
4. Reports evaluated at least one FIT kit that is licensed by Health Canada for use in Canada.
5. Reports excluded symptomatic participants.

Quality Assessment of Included Evidence

An assessment of study quality was performed for all the included evidence. For RCTs, no specific instrument was used, but items such as randomization, sample size estimates and power calculation, and funding sources were reported on. The Expert Panel recognizes that, due to the nature of the studies being examined, blinding to the intervention was not always possible, and therefore the lack of blinding was not considered a methodological flaw, nor was lack of a reported period of follow-up.

For the other evidence types, the Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS) tool was used where appropriate (12). The QUADAS tool is a 14-item questionnaire intended to assess primary studies of diagnostic utility for systematic reviews. The QUADAS instrument can only be used to assess studies of diagnostic utility where one test is compared with another (typically, the gold standard). For diagnostic studies without a comparator, no formal quality assessment was planned.

RESULTS

A total of eleven papers were retained, comprising two systematic reviews (13,14), five papers reporting on three RCTs (15-19), and papers regarding four other studies (20-23). The two systematic reviews retrieved in the literature search, Whitlock et al (14) and Mujoomdar et al (13) identified studies that were also retrieved in the literature search. Whitlock et al (14) is a systematic review commissioned by the United States (US) Preventive Services Task Force (USPSTF) to provide updated recommendations on CRC screening with the development of newer tests; the relevant data from this paper have been incorporated into this review and referenced from the primary sources. Mujoomdar et al (13) is a systematic review commissioned by the Canadian Agency for Drugs and Technologies in Health (CADTH) to analyse the evidence available on the accuracy and compliance of FIT compared to gFOBT in CRC screening. Again, the relevant data from this paper have been incorporated into this review from the primary sources.

A laboratory study by Lamph et al (24) conducted on behalf of the National Health Service (NHS) in the UK reported on an independent assessment of several parameters of FITs, especially temperature stability. Of the three tests evaluated, one, the OC-Sensor product, is approved in Canada. All the findings are reported here in the Results section.

Four additional papers were also obtained and retained for discussion purposes (25-28). Two were U.S. studies that did not meet the inclusion criteria: Rex et al (28) for the American College of Gastroenterology, Levin et al (27) for the American Cancer Society, U.S.

Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Halloran et al (25), for the European Guidelines for quality assurance in colorectal cancer screening, did meet the inclusion criteria, but the full publication appeared after the end date of our search (June 2010). The fourth paper, from the Health Council of the Netherlands (26) did not meet our inclusion criteria. Although retained for discussion purposes, no quality assessment was performed on these reports as no formal adaptation was planned.

Quality of Included Studies

As described previously, RCTs were assessed for quality according to the following criteria: randomization, details of the statistical analysis, expected effect size and details of the statistical power calculation, differences in patient characteristics, and funding sources (Table 3).

The RCT reported by Hoffman et al (15) randomized patients to either FIT or gFOBT using an on-line random number generator. The primary outcome was screening adherence (subsequently referred to here as participation). The two groups were compared using the t-test or the Wilcoxon two-sample test (for continuous variables) and the X^2 test (for categorical variables). Participation (defined as test completion within 90 days) was compared using X^2 and multivariate logistic regression (adjusted stepwise for demographics [age, sex, race/ethnicity, and clinic site], previous testing, and co-morbidities). The expected effect size was a 10% difference in screening participation. Statistical power was determined using the results of a pilot study showing 40% participation with gFOBT; therefore, to detect a 10% difference with 80% power, a minimum of 800 participants was required. The actual number of participants was 404, and it is unclear from the report why the minimum number of participants was not included. Differences in patient characteristics were reported, and no differences between groups were detected. The Department of Veterans Affairs (US) was the source of funding.

The RCT reported by Hol et al in two publications (16,17) randomized participants into three groups, FIT, gFOBT, and FS, on a 1:1:1 basis using a computer generated algorithm. Participants were stratified by age, sex, and socioeconomic status (SES). The primary outcome was participation. Detection of advanced neoplasia (defined as those with either CRC or advanced adenoma [AA]) was the secondary outcome. The three groups were compared using the X^2 test to detect differences in proportions, the t-test to detect differences in means between screening strategies, and univariate logistic regression to detect differences in participation between the three screening strategies, with multivariate modelling used to investigate possible interactions. The expected effect size was 2% difference in participation between the three screening strategies and a 2.5% difference in participation between a maximum of three equal-sized subgroups per arm. Based on an expected 50% participation, the sample size was calculated using 80% power (the exact sample size needed was not explicitly stated). Differences in patient characteristics were reported, and were detected for the following comparisons: sex (more women in FIT and FS arm), age 50-59 (more in FIT and FS arm), age 65-74 (more in FS arm), SES middle (more in gFOBT arm), SES high (more in FIT and FS arm), urban (more in gFOBT arm), rural (more in gFOBT arm compared with FIT and FS; more in FIT compared with FS) (all differences reported $p<0.05$). The Dutch Cancer Society, Dutch Ministry of Health (Health Care Prevention Program), Olympus Medical Systems, and Eiken Chemical were sources of funding.

The RCT reported by van Rossum et al in two publications (18,19) randomized participants by postal address to either FIT (OC-Sensor, n=10,322) or gFOBT (Hemoccult II, n=10,301) using a study specific randomization program. The primary outcome was CRC detection. Differences for participation, positivity, detection, PPV, and specificity were calculated using a two-group X^2 test reported with a 95% confidence interval (CI). The

expected effect size was a 0.3% difference in CRC detection. In order to detect this difference at 80% power, a sample size of 10,000 in each group was needed, but it is unclear whether this number refers to persons invited or to persons that participated. Although 20,623 participants were randomized and invited, 10,993 participated (4,836 gFOBT; 6,157 FIT). Differences in patient characteristics were reported, with no differences observed. The Netherlands Organization for Health Research & Development was the funding source.

The Expert Panel did not detect major methodological flaws in the three RCTs included in this review.

For the studies on diagnostic accuracy, the QUADAS instrument was used for quality assessment (12). QUADAS requires a test of diagnostic accuracy with an appropriate comparator, and neither of the Grazzini et al studies (21,22) compared FIT with either colonoscopy or a gFOBT. Only the studies reported by Allison et al (20) and Park et al (23) were assessed for quality using QUADAS. A summary of the QUADAS results follows. Both Allison and Park studied a group that was representative of the types of participants that would receive screening in practice and had clearly defined selection criteria. The reference standards used for each study were different, with Allison comparing FIT with gFOBT and with Park comparing FIT with colonoscopy. In both studies, the reference standard and the index test were performed in a short enough time period to ensure the target condition would not have changed. For Allison et al, colonoscopy was not used as the comparator to FIT, although participants with a positive test were referred for colonoscopy, and those with a negative test were referred for FS. For Park et al, FIT results were compared directly with colonoscopy results. For both studies, the index test was independent of the reference standard used. The methods describing the use of the reference standard (gFOBT) used in the Allison et al study were not described well enough in the Methods section to allow replication of the procedure by others, while the Park et al study fully described the colonoscopy procedure used allowing replication. Neither study reported whether the results of the index test or the reference standard were assessed independently. The clinical data collected in the study reported by Allison et al would be available in clinical practice, but this was not clear from the Park et al study as details of all the clinical data collected were not provided. Both studies reported on uninterpretable results and how withdrawals from the study were handled and reported. As both Park et al and Allison et al are studies that report on the diagnostic utility of FIT versus other diagnostic tests, no power calculation was described, and no primary outcome was identified. Details of the QUADAS assessment appear in Appendix E.

Table 3. Literature search results.

Authors	Fecal tests	Outcomes reported
RCTs		
van Rossum LG et al, 2008 (19)	Hemoccult II (Beckman Coulter, USA) vs. OC-Sensor (Eiken, Japan)	Primary outcome for which the trial was powered: CRC detection. Other outcomes: specificity, positivity, PPV, participation, detection of CRC and AA.
van Rossum LG et al 2009 (18) *Note: this is further analysis of the same data set used in the 2008 van Rossum paper (19)*	Hemoccult II (Beckman Coulter, USA) vs. OC-Sensor (Eiken, Japan)	Specificity of the OC-Sensor FIT at different cut-off levels in hemoglobin concentration (ng/ml)
Hoffman RM et al, 2010 (15)	Hemoccult II (Beckman Coulter, USA) vs. OC-Micro (Eiken, Japan)	Primary outcome for which the trial was powered: participation (adherence).

Hol L et al, 2009 (17)	Hemoccult II (Beckman Coulter, USA) vs. OC-Sensor Micro (Eiken, Japan)	Primary outcome for which the trial was powered: participation Other outcomes: specificity, positivity, PPV, CRC and AA detection.
Hol L et al, 2010 (16) *Note: this is further analysis of the same data set used in the 2009 Hol paper* (17)	Hemoccult II (Beckman Coulter, USA) vs. OC-Sensor Micro (Eiken, Japan)	Specificity, positivity and PPV at different cut-offs in hemoglobin concentration (ng/ml)
Other studies		
Allison JE et al, 2007 (20)	Hemoccult Sensa (Beckman Coulter, USA) vs. FlexSure OBT/Hemoccult ICT (Beckman Coulter, USA)	Primary outcome: advanced neoplasia (defined as CRC or AA) in the distal colon. Other outcomes: specificity, positivity and PPV in testing 3 consecutive bowel movements
Grazzini G et al, 2009 (22)	OC-Hemodia and OC-Sensor Micro(Eiken, Japan)	Positivity and PPV comparing a 1 vs. 2 day sampling strategy at different cut-off levels in hemoglobin concentration (ng/ml)
Park D et al, 2010 (23)	Hemoccult II (Beckman Coulter, USA) vs. OC-Sensa Micro (Eiken, Japan)	Primary outcome: detection of advanced neoplasia Other outcomes: specificity, positivity and sensitivity in testing 3 consecutive bowel movements at different cut-off levels in hemoglobin concentration (ng/ml)
Grazzini G et al, 2010 (21)	OC-Sensor (Eiken, Japan)	Effect of seasonal temperature variation on positivity and PPV.

Note: RCT(s)– Randomized Controlled Trial(s), PPV–Positive Predictive Value; vs., versus.

RESULTS: Evidence Concerning the Three Key Aspects of FIT Kit Use

FIT Performance Factors

Literature Search Results

Comparing the Performance of FIT to gFOBT

Here we report on the four papers that provided a comparison of FIT performance (at the manufacturer's recommended cut-off level of 100 ng/ml in hemoglobin concentration) to gFOBT (17,19,20,23). Although the focus of the Expert Panel was on the performance of FIT for detecting CRC, when included papers also reported on the detection of advanced adenomas (precancerous lesions that have the potential to develop into CRC if left untreated), the data on advanced adenomas (AA) were also included.

The RCT conducted by van Rossum et al (19) was a study of 20,623 men and women 50–75 years of age. The study compared the performance of Hemoccult II over three days in 10,301 participants to the performance of one OC-Sensor sample in 10,322 participants. If one of the samples tested positive either through Hemoccult II giving a visual colour reaction or the OC-Sensor output giving a numeric value higher than 100 ng/ml as recommended by the manufacturer, participants were referred for follow-up colonoscopy. Participants with negative tests did not undergo follow-up colonoscopy. Tests were returned to the laboratory

via the postal system, and, if not returned immediately, participants were advised to refrigerate the sample. Once at the laboratory, tests were stored at 4˚C if not developed immediately. Of the returned tests, 75% were developed within two days of receipt at the laboratory, and 99.6% of tests were developed within six days. The definition of AA used by van Rossum et al was adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 20%.

The RCT conducted by Hol et al (17) was a study of 10,011 men and women aged 50-74 years. The results for 5,004 people who completed the Hemoccult II gFOBT over three days were compared to the results for 5,007 people who completed one sample for the OC-Sensor FIT. Tests were returned to the laboratory via the postal system. Positivity was defined as at least one positive panel identified by a visual colour reaction from Hemoccult II or a numeric output greater than 100 ng/ml for OC-Sensor. All persons with a positive Hemoccult II were referred for follow-up colonoscopy, as were those who received a numeric output greater than 50 ng/ml with the OC-Sensor test. No information was provided about the time between sampling and test development. The definition of AA used by Hol et al was adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 25%.

The study conducted by Park et al (23) enrolled 770 men and women aged 50 to 75 years who underwent screening colonoscopy in the week after completing the fecal testing. The primary outcome was advanced neoplasia (AN) (defined as either CRC or AA) in the colon or rectum (if the cecum was not reached, the patient was excluded from analysis). The study compared three days of sampling using the Hemoccult II gFOBT to three days of sampling using the OC-Sensor FIT. A positive test was considered to be either one of the Hemoccult II samples exhibiting a visual colour reaction or a numeric output from OC-Sensor greater than 100 ng/ml in at least one sample. No information was provided regarding how samples were returned to the laboratory. All Hemoccult II samples were developed on the day of receipt in the laboratory and OC-Sensor samples were stored at 4˚C until sent to the central analysis centre within two days and processed immediately. All samples were developed within two weeks of the first sample collection date. All participants, regardless of result, underwent colonoscopy, allowing for the measurement of sensitivity. The definition of AA used by Park et al was tubular adenomas ≥ 10 mm or tubulovillous or villous adenomas, or those with high-grade dysplasia regardless of size.

In the study conducted by Allison et al (20), 7,394 men and women 50 years of age and older completed both a gFOBT (Hemoccult SENSA) and a FIT (Hemoccult ICT). Hemoccult SENSA differs from the standard gFOBT (e.g., Hemoccult II) as it is more sensitive for detecting CRC (29,30). The primary outcome was AN (defined as either CRC or AA) of the distal or left colon (rectum, sigmoid, descending). Each participant collected a sample over three days, and the samples were tested using both the gFOBT and the FIT. Originally the Hemoccult ICT was only developed if the Hemoccult SENSA had tested positive in at least one of three samples taken. This was changed during the study so that the three Hemoccult ICT samples were developed regardless of the Hemoccult SENSA result. Tests were returned to the laboratory via the postal system and were developed within five days of the first sample. All Hemoccult SENSA were developed at least three days after the first sampling date. All Hemoccult ICT were developed within 14 days of the first sampling date. All participants whose stools tested positive were referred for follow-up colonoscopy, and all participants whose stools tested negative were referred for FS, allowing the investigators to compare the sensitivity of gFOBT and FIT for the detection of CRC in the distal colon. The definition of AA used by Allison et al was tubular, villous, or tubulovillous adenomas ≥ 10 mm.

Table 4 summarizes data extracted from these studies in relation to the performance characteristics of fecal testing, including sensitivity, specificity, positivity, and PPV.

In the RCT conducted by Van Rossum et al (19), positivity was statistically significantly higher for FIT than for gFOBT (FIT 5.5% vs. gFOBT 2.4%, p<0.01). The specificity for the detection of CRC and AA was significantly lower for FIT than for gFOBT (CRC–FIT 95.8% vs. gFOBT 98.1%, p<0.01; AA–FIT 97.1% vs. gFOBT 98.7%, p<0.01). The difference in PPV for both CRC and AA was not statistically significant when comparing FIT (CRC, 8.6%; AA, 37.9%) to gFOBT (CRC, 10.7%; AA, 39.8%). Although the authors were unable to assess sensitivity, they reported on the percentage of persons in whom CRC and AA were detected in each arm of the trial. Using an intention-to-screen analysis, 0.6% of those in the gFOBT arm had either a CRC or AA detected, compared with 1.4% in the FIT arm. This difference was statistically significant, as was the difference in the per protocol analysis.

In the RCT conducted by Hol et al (17), positivity was statistically significantly higher for FIT than for gFOBT (FIT 4.8% vs. gFOBT 2.8%, p<0.05). The specificity for CRC when using FIT (95.8%) was slightly lower than that for gFOBT (97.6%); however, this difference was not statistically significant. The specificity of FIT for AA was statistically significantly lower than that of gFOBT (FIT 97.8% vs. gFOBT 98.5%, p<0.05). The difference in PPV for both CRC and AA was not statistically significant when comparing FIT (CRC, 10%; AA, 53%) to gFOBT (CRC, 10%; AA, 45%). Although the authors were unable to assess sensitivity, they reported on the percentage of persons in whom CRC and AN were detected in each arm of the trial. Of those in the gFOBT arm, 0.3% had CRC detected and 1.2% had AN detected, compared to the FIT arm in which 0.5% had CRC detected and 2.5% had AN detected. The difference was statistically significant for the detection of AN but not for CRC.

In the study conducted by Park et al (23), positivity was slightly higher for FIT (11.2%) than for gFOBT (7.9%), but this difference was not statistically significant. The difference in specificity for both CRC and AA was not statistically significant when comparing FIT (CRC, 90.1%; AA, 90.6%) to gFOBT (CRC, 92.4%; AA, 92.4%). Again, the difference in PPV for both CRC and AA was not statistically significant when comparing FIT (CRC, 12.8%; AA, 23.3%) to gFOBT (CRC, 6.7%; AA, 13.1%). The sensitivity for detecting CRC was statistically significantly increased when using FIT compared to gFOBT (FIT 92.3% vs. gFOBT 30.8%, p<0.01). The sensitivity of FIT (33.9%) compared to gFOBT (13.6%) for detecting AA was significantly higher at p<0.05.

In the study conducted by Allison et al (20), positivity was statistically significantly lower for FIT than the sensitive gFOBT used in the study (FIT 3.2% vs. gFOBT 10.1% ,p<0.01). The specificity for both CRC and AA was statistically significantly higher for FIT than for gFOBT (CRC–FIT 96.9% vs. gFOBT 90.1%, p<0.01; AA–FIT 97.3% vs. gFOBT 90.6%, p<0.01). The PPV for both CRC and AA was also statistically significantly higher for FIT compared to gFOBT (CRC–FIT 5.2% vs. gFOBT 1.5% p<0.01; AA–FIT 19.1% vs. gFOBT 8.9%, p<0.01). The difference in sensitivity for detecting CRC and AA was not statistically significant for FIT (CRC, 81.8%; AA, 29.5%) compared to gFOBT (CRC, 64.3%; AA, 41.3%).

In summary the sensitivity of FIT for detecting CRC and AA compared to a standard gFOBT, which was assessed in only one study, is superior. In the two Dutch RCTs, specificity was decreased for CRC and AA when using FIT compared to gFOBT. On the other hand, these two studies reported higher AN detection rates for FIT compared with gFOBT. The PPV for detecting CRC and AA using FIT is not different from the standard gFOBT. In general, the positivity rates for FIT using the manufacturer's standard cut-off level in hemoglobin concentration are higher than for Hemoccult II.

Table 4. Performance characteristics of FIT compared with gFOBT.

Publication	Study Population	Comparisons	Sensitivity (%)	Specificity (%)	Positivity (%)	PPV (%)
Van Rossum LG et al, 2008 (19)	20,623 participants aged 50–75	OC-Sensor FIT (n=10,322) vs. Hemoccult II gFOBT (n=10,301)	NR	CRC FIT:95.8 gFOBT:98.1 AA[1] FIT:97.1 gFOBT:98.7	FIT: 5.5 gFOBT:2.4	CRC FIT: 8.6 gFOBT:10.7 AA[1] FIT:37.9 gFOBT:39.8
Hol L et al, 2009 (17)	10,011 participants aged 50-74	OC-Sensor FIT (n=5,007) vs. Hemoccult II gFOBT (n=5,004)	NR	CRC FIT: 95.8 FOBT: 97.6 AA[2] FIT:97.8 gFOBT:98.5	FIT: 4.8 gFOBT:2.8	CRC FIT: 10 gFOBT:10 AA[2] FIT:53 gFOBT:45
Park D et al, 2010 (23)	770 participants aged 50-75 completed both tests concurrently	OC-Sensor Micro FIT vs. Hemoccult II gFOBT	CRC FIT: 92.3 gFOBT: 30.8 AA: FIT:33.9 FOBT:13.6	CRC FIT:90.1 gFOBT:92.4 AA[4] FIT: 90.6 gFOBT:92.4	FIT: 11.2 gFOBT:7.9	CRC FIT:12.8 gFOBT:6.7 AA[4] FIT:23.3 gFOBT: 13.1
Allison JE et al, 2007 (20)	5,932 participants aged ≥50 completed both tests concurrently	FlexSure OBT/Hemoccult ICT FIT vs. Hemoccult Sensa gFOBT	CRC FIT: 81.8 gFOBT: 64.3 AA: FIT:29.5 FOBT:41.3	CRC FIT:96.9 gFOBT:90.1 AA[3] FIT: 97.3 gFOBT:90.6	FIT: 3.2 gFOBT:10.1	CRC FIT:5.2 gFOBT:1.5 AA[3] FIT:19.1 gFOBT: 8.9

Note: CRC–colorectal cancer; AA–advanced adenoma; NR–not reported. All results at manufacturers' suggested cut-off (100 ng/ml).
1 adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 20%
2 adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 25%
3 tubular, villous, or tubulovillous adenomas ≥ 10 mm
4 tubular adenomas ≥ 10 mm or to tubulovillous or villous adenomas, or those with high-grade dysplasia regardless of size

Single-Sample Testing Compared to Multiple-Sample Testing Using FIT

Only one paper compared the results, using FIT, of taking multiple samples from consecutive stools to taking one sample from one stool (22). The data from this study are summarized in Table 5.

In this study by Grazzini et al (22), a single daily sample was compared with testing two samples taken from consecutive bowel movements, using OC-Hemodia at the manufacturer's recommended cut-off level in the hemoglobin concentration of 100 ng/ml. While the samples were taken from consecutive bowel movements, the results were reported as a comparison of a one-day sampling versus a two-day sampling strategy, and both samples had to be positive to be considered a positive result. Positivity was statistically significantly higher when using a one-day strategy compared to a two-day strategy (4.5% vs. 2.3%, $p<0.01$). When the definition of a positive result was changed in the two-day strategy to at least one positive test giving a positive result, overall positivity was statistically significantly higher with the two-day strategy (Two-day, at least one sample positive: 6.7% vs. one-day strategy: 4.5% vs. Two-day, both samples positive: 2.3%; $p<0.01$). There was no statistically significant

difference in the PPV with either of the sampling strategies (1-day, 6.9%; 2-day, 10.4%) or when at least one positive test in a two-day strategy was considered positive overall (5.7%). Specificity and sensitivity were not reported.

In summary, positivity rates were affected by the sampling strategies used. As expected, a two-day strategy where both tests have to be positive resulted in the lowest positivity rate, while a two-day strategy where only one test had to be positive resulted in the highest positivity rate. A one-day strategy resulted in an intermediate positivity rate.

Table 5. Test characteristics for the detection of colorectal cancer using FIT in multiple sampling.

Publication	Study population	Test type	Comparison	Positivity (%)	PPV for CRC (%)
Grazzini G et al 2009 (22)	20,596 participants aged 50–69	OC-Hemodia	1 test positive	4.5	6.9
			At least one test positive	6.7	5.7
			2 tests positive	2.3	10.4

Note: CRC– colorectal cancer

Performance of FIT at Different Cut-off Levels

Here we report on the performance on FIT at multiple hemoglobin concentration cut-off levels that differ from the manufacturer's recommendations. Results from four papers comprising two RCTs (17,18) and two other studies (22,23) are summarized in Table 6.

The RCT reported by van Rossum et al (18) recorded an increasing trend for the specificity of detecting CRC and AA as a combined outcome as the hemoglobin concentration cut-off level increased, but no statistical test results were reported.

In the RCT by Hol et al (17), there was a statistically significant increase in specificity and PPV for detecting both CRC and AA as the hemoglobin concentration cut-off level increased. Positivity was statistically significantly decreased with an increase in hemoglobin concentration cut-off level. FIT was superior to FOBT for CRC detection at $\geq$ 50 ng/mL and $\geq$ 75 ng/mL and for AA detection at $\geq$ 50 ng/mL, $\geq$ 75 ng/m, and $\geq$ 100 ng/mL ($p<0.05$ for all).

The study by Grazzini et al (22) reports that positivity decreased as the cut-off level increased, while PPV increased. The statistical significance of the differences was not reported. The definition of AA used by Grazzini et al was any adenoma $\geq$ 10 mm, and/or a villous component $\geq$ 21%, and/or severe dysplasia.

The study by Park et al (23) reports on the effect of increasing the hemoglobin concentration cut-off level on FIT sensitivity. The authors report that from ≥50 ng/ml to ≥100 ng/ml sensitivity for CRC is unchanged at 92.3% but that above a 100 ng/ml cut-off level sensitivity decreases to 84.6%. For AA there is a decreasing trend for sensitivity as the hemoglobin concentration cut-off level increases. This study also reports an increasing specificity for detecting CRC and AA as the hemoglobin concentration cut-off level increases, but does not report whether these differences are significant. The study data provided for positivity and PPV were insufficient to assess the effect of increasing the hemoglobin concentration cut-off levels.

In summary, these four studies showed that increasing the hemoglobin concentration cut-off level decreased the positivity rate and increased specificity and PPV. In addition, one study reported that increasing the cut-off level above 100 ng/ml decreased sensitivity.

Table 6. Performance characteristics of FIT at different cut-offs levels in hemoglobin concentration.

Publication	Study Population	Cut-off values	Sensitivity (%)		Specificity (%)		Positivity (%)	PPV (%)	
van Rossum et al, 2009 (18)	428 participants 50–75 yr using OC-Sensor				CRC + AA[1]			CR	AA[1]
		≥50 ng/ml	NR		96		8.5	C	NR
		≥75 ng/ml	NR		97.1		NR	NR	NR
		≥100 ng/ml	NR		97.8		NR	NR	NR
		≥125 ng/ml	NR		98.1		NR	NR	NR
		≥150 ng/ml	NR		98.3		NR	NR	NR
		≥175 ng/ml	NR		98.4		NR	NR	NR
		≥200 ng/ml	NR		98.6		NR	NR	NR
		≥225 ng/ml	NR		98.7		NR	NR	NR
								NR	
Hol L et al 2009 (17)	5007 participants aged 50-74 using OC-Sensor				CRC	AA[2]		CR	AA[2]
		≥50 ng/ml	NR		92.9	95.5	8.1	C	
		≥75 ng/ml	NR		95.0	97.2	5.7	7	42
		≥100 ng/ml	NR		95.8	97.8	4.8	9	49
		≥125 ng/ml	NR		96.3	98.2	4.1	10	53
		≥150 ng/ml	NR		96.6	98.4	4.0	11	57
		≥175 ng/ml	NR		97.0	98.7	3.6	11	60
		≥200 ng/ml	NR		97.1	98.8	3.5	12	63
								12	62
Grazzini G et al 2009 (22)	20,596 participants aged 50-69				CRC	AA[3]		CR	AA[3]
		≥80 ng/ml	NR		NR	NR	5.5	C	NR
		≥100 ng/ml	NR		NR	NR	4.5	5.9	NR
		≥120 ng/ml	NR		NR	NR	4.0	6.9	NR
								7.6	
Park D et al 2010 (23)	770 participants aged 50-75 Using OC-Sensor Micro		CRC	AA[4]	CRC	AA[4]		CR	AA[4]
		≥50ng/ml	92.3	44.1	87.2	88.3	NR	C	NR
		≥75ng/ml	92.3	37.3	89.0	89.7	12.2	NR	NR
		≥100ng/ml	92.3	33.9	90.1	90.6	11.2	NR	23.3
		≥125ng/ml	84.6	28.8	91.3	91.6	NR	12.	NR
		≥150ng/ml	84.6	27.1	91.9	92.1	NR	8	NR
								NR	
								NR	

Note: CRC– colorectal cancer; AA–advanced adenoma; NR–not reported.
1 adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 20%
2 adenomas ≥ 10 mm with high-grade dysplasia or with a villous component ≥ 25%
3 adenoma ≥ 10 mm, and/or a villous component ≥ 21%, and/or severe dysplasia
4 tubular adenomas ≥ 10 mm or to tubulovillous or villous adenomas, or those with high-grade dysplasia regardless of size

Information Provided in Test Kit Instructions Results

No further information on the outcomes of interest was identified in the manufacturer inserts and/or documentation.

FIT Kit Usability

Literature Search Results

How does FIT compare with gFOBT in user acceptability?

Three RCTs (15,17,19) that reported comparative data for screening participation rates using FIT versus gFOBT are summarized in Table 7.

In the RCT conducted by van Rossum et al (19), half the study population was given the gFOBT Hemoccult II (n=10,301) and the other half was given the FIT OC-Sensor (n=10,322) to complete. The Hemoccult II test required two samples from a stool on three separate days and involved the smearing of feces onto a card using an applicator stick that then had to be discarded. The OC-Sensor test required one sample from one day and involved scraping the stool sample with a probe that was then inserted into a vial of buffer solution. No dietary or medication restrictions were imposed during the study.

In the RCT conducted by Hoffman et al (15), half the study population was given the gFOBT Hemoccult II (n=202) to complete, and the other half was given the FIT OC-Auto (n=202) to complete. The Hemoccult II test required one sample on three separate days and involved the smearing of feces onto a card using an applicator stick that then had to be discarded. The OC-Auto test required two samples from two consecutive stools and involved scraping the stool sample with a probe that was then inserted into a vial of buffer solution. The Hemoccult II study population were instructed to avoid non-steroidal anti-inflammatory drugs, as well as rare meat, foods containing peroxidase, and vitamin C during the three days of sampling.

In the RCT conducted by Hol et al (17), half the study population was given the gFOBT Hemoccult II (n-5,004), and the other half was given the FIT OC-Sensor (5,007) to complete. The Hemoccult II test required one sample on three separate days and involved the smearing of feces onto a card using an applicator stick that then had to be discarded. The OC-Sensor test required one sample from one day and involved scraping the stool sample with a probe that was then inserted into a vial of buffer solution. No dietary or medication restrictions were imposed during the study

In summary, all three RCTs reported significantly higher participation rates with FIT compared with gFOBT. This increased participation rate for FIT may be attributed to a simpler collection method with fewer samples required, less stool handling, and no need for stick disposal In addition, Hoffman et al (15) required dietary and medication restrictions in the gFOBT group, which could have led to decreased participation.

Table 7. Screening participation rates.

Publication	Study Population	Comparisons	Participation rate (%)
Van Rossum LG et al, 2008 (19)	20,623 participants aged 50-75	Hemoccult II (N=10,301) vs. OC-Sensor (N=10,322)	FIT: 59.6, gFOBT: 46.9; p<0.01
Hoffman RM et al, 2010 (15)	404 participants, two samples taken.	Hemoccult II (N=202) vs. OC-Auto (N=202)	FIT: 68%, gFOBT:55%; p=0.01
Hol L et al, 2009 (17)	10,011 aged 50-74	Hemoccult II (N=5,004) compared with OC-Sensor (N=5,007)	FIT: 61.5, gFOBT: 49.5; p<0.05

Information Provided in Test Kit Instructions Results

Number and Timing of Samples Collected

The manufacturers of most of the approved tests recommend that one sample be collected from one bowel movement. The instructions for the Hemoglobin NS-Plus test from Alfresa recommend two samples collected across two days, and those for the Hemoccult ICT

test from Beckman Coulter recommend three samples across three days. These results are summarized in Table 8.

Diet and Medication Restrictions

Three of the 13 FIT kits provided instructions advising restrictions on alcohol and discontinuation of aspirin and similar medications for 48 hours before stool sampling. These results are summarized in Table 8.

Table 8. Diet and medication restrictions.

Manufacturer / Distributor	Device	Diet/Medication Restrictions	Number of samples/d
Eiken / Polymedco	OC-Auto Micro 80 FOB Test System (believed equivalent to OC-Hemodia)	None noted.	1/d
Eiken / Polymedco	OC-Sensor DIANA IFOB Test System (Assumed the same as OC-Micro)	None noted.	1/d
Alfresa Pharma Corp / Inverness Medical	I-FOBT Hemoglobin NS-Plus	None noted.	1/d for 2d
Beckman Coulter	Hemoccult ICT, Immunochemical Fecal Occult Blood Test (A.K.A. Flexsure OBT)	None noted.	1/d for 3d
Eiken / Polymedco	OC-Light Manual IFOBT	Insert/instructions not available.	1/d
Inverness Medical	Clearview Ultra FOB Test	None noted.	1/d
Medix Biochemica	Actim Fecal Blood Test	Insert/instructions not available.	Unclear, but appears to be 1/d
PSS World Medical	Consult Diagnostic Occult Blood Test Extra Sensitive	Insert/instructions not available.	*Unknown*
Artron	One Step Fecal Occult Blood Test	None noted.	1/d
IND Diagnostic / BTNX	Rapid Response One-Step Fecal Occult Blood Test	Alcohol, aspirin, and similar medications should be discontinued for 48 hours prior to sample collection.	1/d
Tremblay-Harrison	Minute Lab Fecal Occult Blood Test Device	Alcohol, aspirin, and similar medications should be discontinued for 48 hours prior to sample collection.	1/d
WHPM Bioresearch & Technology	Hemosure Immunological Fecal Occult Blood Test	None noted.	1/d
Innovacon	FOB One Step Fecal Occult Blood Test	Alcohol, aspirin, and similar medications should be discontinued for 48 hours prior to sample collection.	1/d

Specimen Stability

Literature Search Results

The stability of hemoglobin in the fecal sample is an issue that has arisen with the vial collection method that characterizes the majority of FITs. Temperature and time are the two variables that play a role in the stability of the stool specimen, requiring consideration when implementing a population-based CRC screening program using FIT. Two papers reported on the stability of the sample in varying temperatures (21,24); Lamph et al (24) also examined the effect of time at selected temperatures.

The study reported by Grazzini et al (21) indirectly measured the effects of ambient temperature and moisture on collected samples in a screening study in an Italian population across different seasons. In this study, the PPV for the detection of CRC and AA did not vary significantly from season to season, ranging from 24% to 26%. However, in a logistic regression analysis that adjusted for age, sex, and history of screening (first or repeated test), the odds of having a positive screening test were significantly lower in summer (Odds Ratio [OR], 0.83; 95% CI, 0.76 to 0.90), autumn (OR, 0.88; 95% CI, 0.83 to 0.94), and spring (OR, 0.90; 95% CI, 0.85 to 0.96) compared to the probability in winter. When the analysis used average ambient temperature in the five to 11 days before the test analysis, an increase of 1° C resulted in a 0.7% reduced odds of a positive FIT (OR, 0.993; 95% CI, 0.989 to 0.996). The authors concluded that in summer the probability of detecting CRC or AA is about 13% lower than in winter. This study reported a mean of 11 days between sample collection and laboratory development but did not analyse the effects of time and temperature together.

Lamph et al (24) conducted an independent evaluation of the temperature stability of the OC-Sensor product and subsequently verified the manufacturer's reported temperature stability values. Table 9 summarizes these data.

Table 9. FIT kit temperature stability as measured by Lamph et al (24) for the OC-Sensor kit.

Storage temp (°C)	Manufacture Claimed Stability versus measured stability, in days	
-18 to -24	claimed	10-14
	measured	agree
4 to 8	claimed	7
	measured	agree
23 to 26	claimed	3
	measured	agree
29 to 34	claimed	No claim made
	measured	<3

Information Provided in Test Kit Instructions Results

Table 10 provides details on temperature stability and storage times and conditions for the 13 Health Canada-approved FIT kits. According to the information provided by the manufacturer, using three of the FITs, specimens are stable for ≥ 7 days (I-FOBT at 25 °C, Hemoccult ICT at 15-30 °C, and Clearview UltraFOB at 2-8 °C) and with two of the FITs samples are stable for ≥ 15 days (OC-Auto at 15-30 °C, OC-Light at 15-30 °C).

Table 10. Specimen stability and temperature information from manufacturers.

Manufacturer / Distributor	Device	Specimen stability and temperature information
Eiken / Polymedco	OC-Auto Micro 80 FOB Test System	Manufacturer states specimens are stable for 15 days at 15-30˚C and 30 days at 2-8˚C. There are also data that show the specimen can be kept for less than 3 days at 29–34˚C but can be kept for at least 10–14 days at -18˚C to -24˚C.
Eiken / Polymedco	OC-Sensor DIANA IFOB Test System	
Alfresa Pharma Corp / Inverness Medical	I-FOBT Hemoglobin NS-Plus	Manufacturer's marketing materials indicate the specimen is 95% stable for 7 days at 25˚C, after two days at 37˚C stability drops to 90% then to 80% after 7 days, stable for 30 days at -40˚C, and after two days at 7˚C stability drops to 90% but stays at this for 20 days.
Beckman Coulter	Hemoccult ICT, Immunochemical Fecal Occult Blood Test (A.K.A. Flexsure OBT)	Manufacturer instructions say specimen is stable after sampling for 14 days at 15–30˚C.
Eiken / Polymedco	OC-Light Manual IFOBT	Manufacturer states the specimen is stable for 15 days at 15–30˚C or 30 days at 2–8˚C.
Inverness Medical	Clearview Ultra FOB Test	Manufacturer states that specimen can be stored at 15–30˚C for up to 5 days or 2–8˚C for up to 14 days.
Medix Biochemica	Actim Fecal Blood Test	Manufacturer states that specimen is stable for up to 7 days at 2–25˚C.
PSS World Medical	Consult Diagnostic Occult Blood Test Extra Sensitive	*Unknown*
Artron	One Step Fecal Occult Blood Test	Manufacturer instructions state the test should be developed immediately and read within 10-15 minutes. No information on storage if not developed immediately.
IND Diagnostic / BTNX	Rapid Response One-Step Fecal Occult Blood Test	Manufacturer instructions state if not developed straight away the specimen is stable up to 7 days at 37˚C. This is intended to be a physician developed test (although not licensed for this currently) but is suitable and licensed for laboratory development.
Tremblay-Harrison	Minute Lab Fecal Occult Blood Test Device	Manufacturer instructions intend for the test to be developed within 6 hours of collecting specimen, if not developed within 6 hours, specimen is stable at 2–8˚C for 3 days .

Manufacturer / Distributor	Device	Specimen stability and temperature information
WHPM Bioresearch & Technology	Hemosure Immunological Fecal Occult Blood Test	Manufacturer instructions intend for the test to be developed by the patient immediately but if not the specimen is stable at 2-8˚C but they do not state for how long
Innovacon	FOB One Step Fecal Occult Blood Test	Manufacturer instructions intend for the test to be developed by the patient within an hour, but if not it will be stable for 3 days at 15-30˚C

Implementing FIT in Population-Based CRC Screening Programs

Recommendations from Other Jurisdictions

Two guidelines from the US were identified. A guideline by Rex et al (28) for the American College of Gastroenterology recommended annual FIT over card-based gFOBT because FIT has both superior test characteristics and adherence rates for the detection of CRC. A guideline by Levin et al (27) for the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology stated that annual testing with either a high-sensitivity gFOBT or FIT in both male and female participants aged 50 years and older are both acceptable options for CRC screening.

In England, the NHS Evaluation Report on "Immunochemical faecal occult blood tests" (24) provided a comparative analysis of three FIT devices available in the UK from their technical performance to the operational considerations and device purchasing procedures. The report concluded that there was no perfect FIT on the market but that the OC-Sensor DIANA analyser, despite not being an ideal test, was the most suitable system for the English Bowel Cancer Screening Program.

The Health Council of the Netherlands report on "A national colorectal cancer screening programme" (26) recommended establishing a nationwide CRC screening program using FIT for 55 to 75 year olds on a biennial basis. The report stated that 50 ng/ml is the optimum positivity threshold in hemoglobin concentration in terms of cost effectiveness, but provisionally recommended a cut-off level of 75 ng/ml because of considerations of colonoscopy capacity required to support the program. A single sampling method was advised due to concerns that increasing sensitivity through multiple sampling may result in decreased participation. The report also recommended that laboratory analysis be organised so that samples could be tested as soon as possible following arrival of the kit, and that, when rapid testing is not possible, the sample should be placed in cold storage.

The European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis (25) state that FITs provide an improvement in the test characteristics over gFOBT due to improved sensitivity and specificity, as well as the ability to automate test development and adjust the concentration at which a positive result is reported. The European Union (EU) Guidelines state that, although FITs are currently the test of choice for population screening, individual device characteristics, including ease of use by the participant and the laboratory, suitability for transport, sampling reproducibility ,and sample stability are important when selecting the FIT device most appropriate to a specific screening program. The EU Guidelines recommend that, until more stability data are published on FIT, screening programs should adopt the conditions and period of storage described in the manufacturer's instructions for use after having determined that they are appropriate for local conditions. They also recommend that consideration should be given to using more than

one specimen together with criteria for assigning positivity that, combined, provide a referral rate which is clinically, logistically and financially appropriate to the screening program. The EU Guidelines state that the proportion of unacceptable tests received in the laboratory should not exceed 3% of all kits received and that less than 1% is desirable. The Guidelines note that the proportion of unacceptable tests is influenced by the ease of use of the test kit and the quality of the test kit instructions for use. They recommend that the laboratory be able to unambiguously identify the subject identification (ID) on the test device, possibly through the use of barcodes. In addition the EU Guidelines recommend that a local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling, and labelling procedures are acceptable.

The recommendations from other jurisdictions are summarized in Table 11.

Table 11: Recommendations for use of FIT in organized CRC screening programs.

Guideline document	Recommendations
Levin et al (27) 2008	• Annual testing with either gFOBT or FIT in both male and female participants aged 50 years and older are both acceptable options for CRC screening
Centre for Evidence-Based Practice in the NHS (24) 2009	• Compared: Hem-SP/MagStream HT, OC-Sensor, FOB, Gold/SENTiFOB, FOB Gold DEVEL-A-TAB • OC-Sensor DIANA analyzer, despite not being an ideal test, most suitable for the English Bowel Cancer Screening Program
Health Council of The Netherlands (26) 2009	• Nationwide screening program using FIT for 55-74 year olds biennially • 50 ng/ml is the optimum cut-off level in hemoglobin concentration in terms of cost-effectiveness • Provisionally recommend cut-off level in hemoglobin concentration of 75 ng/ml due to colonoscopy capacity • Single sampling method advised to maximize positivity • Samples should be tested as soon as possible once returned to the laboratory
Rex et al (28) 2009	• Annual FIT testing is the preferred CRC screening method compared to gFOBT.
European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis (25) 2010	• FIT is preferred over gFOBT for population screening for CRC. FIT factors such as ease of use, transportability, sample reproducibility, and sample stability need to be considered when developing a program • Prior to implementation, a pilot study should be performed to ensure that the FIT kit chosen achieves a positivity rate that is clinically acceptable, logistically, and financially possible • The acceptable loss of completed tests is under 3% of all tests with the goal being less than 1% • Subject IDs should be easily identifiable, possibly through the use of barcodes • Screening programs should adopt manufacturer's storage conditions • A local pilot study of FIT should be conducted before widespread implementation

Implementing FIT in Population-Based CRC Screening Programs in Canada

Nova Scotia

In 2009, Nova Scotia launched a biennial screening program for men and women aged 50 to 74 years using Hemoccult ICT (Beckman Coulter), a card-sampling method with a non-numeric result. Hemoccult ICT was chosen due to cost considerations, its long shelf-life, and

its ability to withstand temperature fluctuations. Currently the program is implemented in all District Health Authorities in Nova Scotia. Participants are invited to participate by letter and receive a FIT kit two weeks later by mail. They complete two samples over two days and return the completed FIT kits by regular post to a single central lab. FIT kits with samples greater than ten days old and kits with no sample collection date are not processed; in these cases, the participant is sent a second FIT kit for completion, along with a letter explaining why the test could not be processed. An evaluation of the program is underway.

Saskatchewan

In 2009, Saskatchewan launched a pilot program in the Five Hills Health Region for men and women between 50 and 74 years of age; an expansion to cover approximately half the province is planned for 2011. The program uses the OC-Auto Micro 80 device (Eiken), a vial-sampling method. Participants are invited by letter to participate and receive a FIT kit three weeks later by mail, with reminders sent after six weeks if the kit has not been completed. Kits are barcoded with name, date of birth, and sex of the participant; the participant also fills out a form that verifies his or her eligibility for screening and identifies the primary care provider to be notified of test results. Eligible (i.e., average risk) participants complete one sample and drop the completed FIT kit at a designated medical laboratory or a Canada Post retail outlet in a supplied postage-paid envelope. Completed kits cannot be sent by regular post. If the sample cannot be dropped off within 24 hours, participants are advised to refrigerate the sample. About 3.5% of kits have been rejected, largely due to the specimen collection date not being marked, expired samples, and damaged kits. An evaluation of the pilot is underway.

British Columbia

In 2009, British Columbia launched a pilot program in Penticton, Powell River, and Vancouver downtown core for men and women aged 50 to 74 years, using the OC-Auto Micro 80 device (Eiken), a vial-sampling method. The participants request a kit through a toll-free number and collect two samples over two days. Participants are advised that the completed kit must be stored in the refrigerator, and not frozen, and returned to a specified drop-off location (designated laboratory, hospital, or physician's office), ideally within one or two days; from there kits are sent to a central processing laboratory in Vancouver by courier. Completed kits cannot be sent by regular post. Results must be analyzed within 15 days after the first sample is collected.

Table 12 summarizes the details of FIT use in Canada.

Table 12: Use of FIT in CRC screening programs in Canada.

Jurisdiction	Stage of implementation	FIT used	Details of sampling and transportation	Details of processing
Nova Scotia	Program is implemented across the province	Hemoccult ICT (card method)	Two samples over two days. Completed kits returned by business reply mail to a single central lab.	Samples over ten days old or with no collection date given are not processed – a letter with explanation along with a second kit is sent to the participant.
Saskatchewan	In pilot phase	OC-Auto Micro 80 (vial method)	Completed kits are dropped off at a medical lab or mailed at a Canada Post retail outlet in a supplied postage-paid	If the sample cannot be dropped off within 24 hours, participants advised to refrigerate sample.

			envelope.	
British Columbia	In pilot phase	OC-Auto Micro 80 (vial method)	Two samples over two days. Completed kits are dropped off at designated locations, couriered to a central lab for processing.	Participants advised to refrigerate sample but not to freeze them until returned. Samples are rejected if received >15 days after first sample taken.

Note: DHA, District Health Authority.

DISCUSSION

The purpose of this evidentiary review is to evaluate the existing evidence concerning FIT to inform the decision on how to replace the current gFOBT with a FIT in Ontario's ColonCancerCheck Program.

FIT Performance Factors

At this time, and in contrast to gFOBT, there is no evidence from RCTs in average-risk screening populations concerning the use of FIT in repeated (annual or biennial) testing. However, gFOBT used in repeated testing (coupled with a colonoscopy for those who screen positive) is associated with a reduction in CRC mortality (4-6). Therefore, the published evidence evaluated here compared the test characteristics of FIT with gFOBT in one-time (not repeated) testing. The assumption is that, if the test characteristics compare favourably, FIT used in a screening program with repeated testing would, at a minimum, achieve the same mortality reduction. A detailed evaluation of the test characteristics of FIT for detecting AA is beyond the scope of this work. However, to the extent that FITs are able to detect AA, the use of FIT for CRC screening holds promise for CRC prevention as well as early detection.

Results from two Dutch RCTs in asymptomatic persons at average risk for CRC show that, compared with a standard gFOBT, the CRC and AA detection rates are greater with FIT but that specificity is lower. The PPVs of FIT and gFOBT for detecting CRC and AA are similar but the positivity rate of FIT (when used according to the cut-off level in hemoglobin concentration recommended by the manufacturer to define a positive test) is greater. Note however, that the positivity rates reported, which were 5.5% and 4.8% in the two Dutch RCTs are comparable to the current positivity rate of 4.7% observed in the ColonCancerCheck Program. The increase in CRC detection is an advantage of FIT compared with gFOBT. In addition, the increase in detection of AA is a key advantage of FIT compared with the standard gFOBT, which does not detect AA. Since AAs are precancerous lesions, the detection of AA (and their removal at colonoscopy) means that FIT use may be associated with CRC prevention. In the Dutch RCTs, only those individuals who had a positive FIT underwent colonoscopy, so sensitivity could not be evaluated. In the study of Allison et al, the investigators compared the sensitivity of gFOBT and FIT for the detection of CRC in the distal colon. In this study the sensitivity of FIT for detecting CRC was greater than for gFOBT, although the difference was not statistically significant. However, because Allison et al used a sensitive gFOBT (HemeSENSA), and not a standard gFOBT, the results cannot be generalized to Ontario, where the ColonCancerCheck program uses a standard gFOBT. The RCT of Park et al reported a superior sensitivity for FIT compared with a standard gFOBT for detecting CRC and AA.

FIT positivity rates are affected by the number of stool specimens sampled and the definition of a positive test. One study compared FIT performance for single versus multiple stool samples and reported that a one-sample method resulted in higher positivity than a two-sample method where both tests had to provide a positive result to be considered positive. A two-sample method where only one test had to provide a positive result to be considered

positive resulted in the highest positivity rate. The recommendations of kit manufacturers vary, but most manufacturers advise a single stool sample.

The two Dutch RCTs used FIT kits that provide a numerical result for hemoglobin concentration and, in additional studies (17,19), reported on the effects of a change in cut-off level in hemoglobin concentration on FIT performance. These results showed that when lower cut-offs in hemoglobin concentration were used to define a positive FIT, the detection of CRC and AA were greater, the specificity and PPV for CRC lower, and the positivity rates were higher. The only study that reported on sensitivity at different cut-off levels in hemoglobin concentration was that of Park et al (23), who reported that sensitivities for CRC and AA were decreased as the cut-off level increased. Based on their results, both groups of Dutch investigators recommended using a cut-off in hemoglobin concentration below the manufacturer's standard cut-off of 100 ng/ml, with one group (18) advising a cut-off of 75 ng/ml. Choosing an optimal cut-off in stool hemoglobin concentration for screening an average-risk population involves weighing the better clinical outcomes (more CRCs and AA detected) associated with lower cut-offs against the higher costs (more colonoscopies required).

All three RCTs reported statistically significantly higher participation rates for FIT compared with gFOBT. The Expert Panel noted that the ColonCancerCheck Program needs to maximize screening participation rates. An evaluation of the factors that affect participation rates was beyond the scope of this review. However, explanations for higher participation rates are linked to kit usability factors, which are discussed below.

In summary, with respect to FIT performance, compared with standard gFOBT, current evidence indicates an increased participation in screening, higher sensitivity for the detection of CRC and AA, and higher rates of detection for CRC and AA. It is important to recognize that detecting AA is a distinguishing feature of FITs compared with standard gFOBTs. These advantages of FIT are offset by a lower specificity for the detection of CRC and AA and a higher positivity rate (when using the manufacturer's cut-off), which in turn may require a greater number of colonoscopies. However, these performance characteristics change when the cut-off level in hemoglobin concentration is changed, allowing a screening program to select the optimal cut-off for the program, balancing the better clinical outcomes (more cancers detected) associated with lower cut-offs against the higher costs (more colonoscopies required).

FIT Kit Usability Factors

Because the FIT is specific for human hemoglobin, there is no interference by dietary substances, and in general, dietary restriction is not advised. No published studies evaluating diet or medication use were identified, although three manufacturers of FIT kits that do not provide a numerical result advised avoidance of alcohol and aspirin and similar medications for 48 hours prior to sample collection. In terms of dietary and medication restrictions, the ColonCancerCheck Program advises only that vitamin C supplements and citrus fruit and juices be avoided for three days prior to and during stool sample collection with gFOBT (9).

Specimen Stability

While sample stability has not been a major issue for gFOBT, it is a consideration with FIT, because of the relative instability of the globin in the collection systems used. Temperature, which can be affected by weather, transport, and storage conditions, affects specimen stability. The study by Grazzini et al (21) in Italy showed that during the warmer summer months the test characteristics of FIT differed from those in the winter months. The authors reported that a 1°C increase in temperature reduced the probability of a positive FIT by 0.7% and that this resulted in a 13% reduction in the probability of detecting a CRC or AA in

summer compared to winter. Because of this, the manufacturers specify storage and transport conditions to minimize the effect of sample instability on FIT performance. In general, compared with gFOBT, the conditions for FIT are more stringent and the time period between sample collection and processing is shorter. Satisfying these more stringent conditions is challenging for organized CRC screening programs.

In summary, specimen stability with regard to temperature and time is an issue that requires consideration and a thorough understanding of the specifications of the FIT device chosen. The Expert Panel discussed the issue of specimen stability given the extreme temperatures that occur in Ontario, and recommend that a pilot study be conducted prior to full implementation, in part to assess specimen stability (see below).

Lessons from ColonCancerCheck

Ontario's ColonCancerCheck Program was launched province-wide in 2008. The Program uses a standard (not high sensitivity) gFOBT (Hemascreen), which has the same test characteristics as the Hemoccult II. This is the same gFOBT currently used in the English Bowel Cancer Screening Program. Participants obtain a gFOBT kit from their primary care provider or, if they do not have one, from a community pharmacy or by calling Telehealth Ontario. Kits are not mailed to participants. Two samples are collected from each of three stools. Participants can return completed kits by regular mail or by drop-off at a participating laboratory. The majority of kits are returned by mail. A positive test is defined as at least one positive sample. The positivity rate has been relatively stable at about 4.7% throughout 2010.

The experience gained over the last two years highlights the importance of specific aspects of program design that are independent of the type of kit used (gFOBT or FIT). Understanding these aspects provides an opportunity for improving the performance of the ColonCancerCheck Program.

According to Ontario regulation, for a laboratory to process a test, the test must be accompanied by a completed, signed requisition form, and both the test and the requisition must contain two matching "unique" patient identifiers, typically name, date of birth, and/or Ontario Health Insurance Number (OHIN). If these conditions are not met, the test will be rejected and not processed by the laboratory. GFOBT kits are also rejected if the specimens are greater than 21 days old (9). GFOBT kits are considered to have an indeterminate result if a window has a negative result but no specimen collection date marked, or if the sample was applied incorrectly to a window. Participants whose kits are rejected for processing or yield an indeterminate result are advised to obtain another kit and repeat the test. The percentage of gFOBT kits rejected for processing has declined from 16% at program launch (2008) to 4% in 2010; still much higher than the EU Guideline recommendation of less than 1% (25). The percentage of kits with indeterminate results has been stable at 6% in 2010. Taken together, then, more than 10% of participants are advised to repeat the test. Many of these initial participants do not subsequently submit a satisfactory sample. This clearly represents a missed opportunity to detect CRC and consumes considerable resources.

The current unacceptably high rate of rejected specimens and indeterminate results is largely due to program design, in particular, the way in which the gFOBT kits are distributed and labelled. Family physicians and/or patients complete the required information (name and date of birth) on both the kit and the requisition; regulations require that this information must match exactly before a laboratory can process a kit. Pre-labelling the kits with unique patient identifiers and eliminating the need for a separate requisition would dramatically reduce the unacceptably high rate of rejected kits and ensure the improved performance of the ColonCancerCheck Program and a better use of resources.

Implementing FIT in Population-Based CRC Screening Programs

In Europe, guidelines have made recommendations for FIT device selection and implementation in population-based CRC screening programs (24-26). Recognising the potential challenges of launching a FIT-based CRC screening program, the guidelines have recommended pilot programs to ensure that all logistical challenges are dealt with before full implementation (25,26).

One Canadian province (Nova Scotia) has achieved province-wide program implementation using a card-based FIT, which is associated with greater specimen stability and is returnable by regular post. In contrast, Saskatchewan and British Columbia are piloting the use of vial-based FITs that cannot be returned by mail because of specimen stability concerns.

Recommendations for Ontario's ColonCancerCheck Program

The Expert Panel concludes that the FIT has the following important advantages compared with the standard gFOBT: higher screening participation rates, greater sensitivity for detecting CRC and AA, potential for automation in the laboratory, and potential to select the cut-off level of hemoglobin concentration that defines a positive test. However, there are the following potential disadvantages: greater specimen instability and possibly higher positivity rates.

The Expert Panel concludes that the ideal FIT would have the following features:

1. Provide a numeric result (so the cut-off level in haemoglobin concentration can be chosen)
2. Be readily automated in the laboratory
3. Require one stool sample
4. Have specimen stability across wide variations in temperature
5. Have specimen stability for at least 7 days between the time of sample collection and processing in the laboratory.

Currently, it is uncertain whether any FIT available in Canada has all these features. The Expert Panel recommends that Ontario's ColonCancerCheck conduct a pilot study to evaluate the performance of one or more FIT kits to guide the selection of a FIT device as well as guide any changes in program design required for FIT implementation. The pilot study would evaluate the FIT kits in the laboratory and in the field. The laboratory component would include an evaluation of specimen stability under varying conditions and the feasibility of using automated processes in a population based program. The field component would evaluate kit distribution, labelling of kits, stool sampling, and transportation of completed kits to the laboratory. An economic evaluation should also be conducted. The intent would be to evaluate these aspects in such a way that when the laboratory and field components are put together, the redesigned program would ensure feasibility and improved performance at an acceptable cost.

Finally, based on findings from the current ColonCancerCheck Program, the Expert Panel strongly recommends changes in program design such that the current approach of manual kit labelling be changed to an automated approach (e.g., using a bar code), and the need for a separate requisition to accompany the kit be dropped. In this way, the performance of Ontario's ColonCancerCheck Program would be improved, and better use would be made of current resources.

CONFLICT OF INTEREST

None declared.

JOURNAL REFERENCE

The following original article has been published in the *Canadian Journal of Gastroenterology* (© 2012 Pulsus Group Inc.; http://www.pulsus.com/journals/journalHome.jsp?jnlKy=2&/):

- Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol. 2012 Mar;26(3):131-47.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario. It is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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Appendix A. FIT Guidelines Expert Panel.

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Appendix B. FIT Test Kits approved by Health Canada.

Manufacturer / Distributor	Device	Class	Product description	Vial / Card sample?	Number of samples	Positive cut-off point	Throughput / Development time	Specimen stability and temperature information	Notes
Eiken / Polymedco	OC-Auto Micro 80 FOB Test System	2	Flat tube, dipstick collection, machine developed	Vial	1 sample across 1 day although some groups use 2 samples across 2 days	Can be set by user. Machine comes set at 100ng/ml	80 samples per hour	Manufacturer states samples are stable for 15 days at 15-30˚C and 30 days at 2-8˚C. There is also data that shows the sample can be kept for less than 3 days at 29–34˚C but can be kept for at least 10–14 days at -18˚C to -24˚C[1].	• Product insert and patient instructions obtained • Being used by BC and Saskatchewan in pilot testing
Eiken / Polymedco	OC-Sensor DIANA IFOB Test System	2	Flat tube, dipstick collection, machine developed	Vial	1 sample across 1 day although some groups use 2 samples across 2 days	Can be set by user. Machine comes set at 100ng/ml	280 samples per hour		• Used OC-Auto product insert and patient instructions
Alfresa Pharma Corp / Inverness Medical	I-FOBT Hemoglobin NS-Plus	2	Flat tube, dipstick collection, machine developed	Vial	2 samples across 2 days	Set by user	300 samples per hour	Manufacturer's marketing materials indicate the sample is 95% stable for 7 days at 25˚C, after two days at 37C stability drops to 90% then to 80% after 7 days, stable for 30 days at -40˚C, and after two days at 7˚C stability drops to 90% but stays at this for 20 days.	• Product insert and marketing slideshow obtained
Beckman Coulter	Hemoccult ICT, Immunochemical Fecal Occult Blood Test (A.K.A. Flexsure OBT)	2	Test card, applicator stick, on card developed	Card	3 samples across 3 days	Unknown	2 min per test	Manufacturer instructions say test is stable after sampling for 14 days at 15-30˚C	• Product insert and patient instructions obtained • Being used by Nova Scotia in pilot testing

Manufacturer / Distributor	Device	Class	Product description	Vial / Card sample?	Number of samples	Positive cut-off point	Throughput / Development time	Specimen stability and temperature information	Notes
Eiken / Polymedco	OC-Light Manual IFOBT	2	Long cylindrical tube, dipstick collection, test strip developed	Vial	1 sample over 1 day	Unknown	5 min per test	Polymedco states the specimen is stable for 15 days at 15-30˚C or 30 days at 2-8˚C	• No product insert obtained, information taken from http://www.ifobt.com/hp_overmanualhtml
Inverness Medical	Clearview Ultra FOB Test	2	Long cylindrical tube, dipstick collection, test strip developed	Vial	1 sample over 1 day	50ng/ml	5 min per test	Manufacturer states that specimen can be stored at 15-30˚C for up to 5 days or 2-8˚C for up to 14 days	• Product insert obtained
Medix Biochemica	Actim Fecal Blood Test	2	Cylindrical tube, sampling stick that then is put into the tube, development occurs on the stick	Vial	Unclear but appears to be 1 sample from 1 day	Unknown	10 min per test	Manufacturer states that specimen is stable for up to 7 days at 2-25˚C	• No product insert obtained, information taken from http://www.bhr.co.uk/actim-fecal-blood-test-procedure-2069-0.html
PSS World Medical	Consult Diagnostic Occult Blood Test Extra Sensitive	2	Unknown	Vial	*Unknown*	*Unknown*	*Unknown*	*Unknown*	• Have not been able to gather information on this test

Manufacturer / Distributor	Device	Class	Product description	Vial / Card sample?	Number of samples	Positive cut-off point	Throughput / Development time	Specimen stability and temperature information	Notes
Artron	One Step Fecal Occult Blood Test	2	Cylindrical tube, dipstick sampling, developed on a cassette	Vial	1 sample from 1 day	50ng/ml	10-15 min per test	Manufacturer instructions state the test should be developed immediately and read within 10-15 minutes. No information on storage if not developed immediately	• Product insert obtained
IND Diagnostic / BTNX	Rapid Response One-Step Fecal Occult Blood Test	2 (applying for class 3)	Cylindrical tube, dipstick sampling, developed on a cassette	Vial	1 sample from 1 day	50ng/ml	5 min per test	Manufacturer instructions state if not developed straight away the specimen is stable up to 7 days at 37˚C. This is intended to be a physician developed test (although not licensed for this currently) but is suitable and licensed for laboratory development.	• Product insert obtained
Tremblay-Harrison	Minute Lab Fecal Occult Blood Test Device	3	Cylindrical tube, dipstick sampling, developed on a cassette	Vial	1 sample from 1 day	50ng/ml	5 min per test	Manufacturer instructions intend for the test to be developed within 6 hours of collecting sample, if not developed within 6 hours, sample is stable at 2-8˚C for 3 days .	• Product insert obtained
WHPM Bioresearch & Technology	Hemosure Immunological Fecal Occult Blood Test	2	Cylindrical tube, dipstick sampling, developed on a cassette	Vial	1 sample from 1 day	50ng/ml	5 min per test	Manufacturer instructions intend for the test to be developed by the patient immediately but if not the specimen is stable at 2-8˚C but they do not state for how long	• Product insert obtained

Manufacturer / Distributor	Device	Class	Product description	Vial / Card sample?	Number of samples	Positive cut-off point	Throughput / Development time	Specimen stability and temperature information	Notes
Innovacon	FOB One Step Fecal Occult Blood Test	2	Cylindrical tube, dipstick sampling, developed on a cassette	Vial	1 sample from 1 day	50ng/ml	10 min per test	Manufacturer instructions intend for the test to be developed by the patient within an hour, but if not it will be stable for 3 days at 15-30°C	• Product insert obtained

Notes:

Device classification 2 means the product is licensed for development in a laboratory setting only, although Health Canada do not regulate this, physicians could develop the test in their office

Device classification 3 means the product is licensed for development at any point of care, which could be physician's office or pharmacy

Reference:

1 NHS. Evaluation report: Immunochemical faecal occult blood tests. November 2009

Appendix C. Definition of diagnostic parameters.

Relationship between screening test result and presence of cancer.

	Cancer Present	
Screening Test Result	Yes	No
Positive test	True positive (a)	False positive (b)
Negative test	False negative (c)	True negative (d)

The definitions used in this guideline are as follows:

True positive (TP): those with a positive screening test and confirmed cancer
(a)

False positive (FP): those with a positive screening test and no confirmed cancer
(b)

True negative (TN): those with a negative screening test and no confirmed cancer
(d)

False negative (FN): those with a negative screening test and confirmed cancer
(c)

Positive predictive value (PPV): proportion of people with a positive screening test who have confirmed cancer
(a/(a+b))

Sensitivity: proportion of people with cancer who have a positive screening test
(a/(a+c))

Specificity: proportion of people who do not have cancer who have a negative screening test
(d/(b+d))

Appendix D. Literature search strategies.

Database: Ovid MEDLINE(R) <1996 to June Week 2 2010>

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1 fecal immunohistochemical test.mp. (0)
2 exp Immunohistochemistry/ or fecal immunochemical test.mp. (263814)
3 screening.mp. or exp Mass Screening/ (182626)
4 colorectal neoplasms.mp. or exp Colorectal Neoplasms/ (67158)
5 2 and 4 (5545)
6 3 and 5 (244)
7 limit 6 to (english language and humans) (227)
8 from 7 keep 1,4,6,10-11,19-20,22,33,35,37-38,40,52,54,66,71-72,76,84,90,95,103,113,115,119,162,184-185,191,218-219,224 (33)

Database: EMBASE <1996 to 2010 Week 23>

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1 fecal immunohistochemical test.mp. (0)
2 exp immunohistochemistry/ or immunohistochemicalmp. (194893)
3 fecal immunochemical test.mp. (14)
4 exp screening/ or exp cancer screening/ or screening.mp. or screening test/ (232254)
5 colon cancer.mp. or exp colon cancer/ (73399)
6 rectal cancer.mp. or exp rectum cancer/ (53138)
7 5 or 6 (81276)
8 2 or 3 (194906)
9 4 and 8 (3172)
10 7 and 8 and 9 (385)
11 limit 10 to english language (362)
12 from 11 keep 5,7,12,16,23,29,33,41-42,46,51,53,59,72,84-86,91,96,107,136,143,161,176,214,244,263,266,301,327,362 (31)

Appendix E. QUADAS results.

Domain	Allison et al, 2007			Park et al, 2010		
	Yes	No	Unclear	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	✓			✓		
2. Were selection criteria clearly described?	✓			✓		
3. Is the reference standard likely to correctly classify the target condition?		✓		✓		
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	✓			✓		
5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?		✓		✓		
6. Did patients receive the same reference standard regardless of the index test result?		✓		✓		
7. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	✓			✓		
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	✓			✓		
9. Was the execution of the reference standard described in sufficient detail to permit its replication?		✓		✓		
10. Were the index test results interpreted without knowledge of the results of the reference standard?			✓			✓
11. Were the reference standard results interpreted without knowledge of the results of the index test?			✓			✓
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	✓					✓
13. Were uninterpretable/ intermediate test results reported?	✓			✓		
14. Were withdrawals from the study explained?	✓			✓		
TOTALS	8	4	2	11	0	3

cancer care ontario | action cancer ontario
program in evidence-based care | programme de soins fondé sur des preuves

Evidence-Based Series 15-8: Section 3

Fecal Immunochemical Tests Compared With Guaiac Fecal Occult Blood Tests for Population-Based Colorectal Cancer Screening: Methodology of the Recommendations Development and External Review Process

L. Rabeneck, R.B. Rumble, F. Thompson, M. Mills, C. Oleschuk, A.H. Whibley, H. Messersmith, and N. Lewis: The FIT Guidelines Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
and the ColonCancerCheck Clinical Advisory Committee, CCO

Report Date: November 8, 2011

THE PROGRAM IN EVIDENCE-BASED CARE

The development of the guidelines was led by the Fecal Immunochemical Test (FIT) Guidelines Expert Panel, a Working Group facilitated by the Program in Evidence-Based Care (PEBC) and the ColonCancerCheck Clinical Advisory Committee. Both of these programs are initiatives of Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and Guideline Development Groups (GDGs), the resulting clinical recommendations, and an external review by Ontario clinicians and others for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series

This Evidence-Based Series (EBS) is comprised of three sections:

- **Section 1: *Recommendations***
  This section contains the standards derived by the FIT Guidelines Expert Panel through a systematic review, an environmental scan, interpretation of the clinical and scientific literature and expert consensus process, as well as through a formalized external review by Ontario and international practitioners and CRC screening experts.

- **Section 2: *Evidentiary Base***
  This section also presents the comprehensive systematic review of the clinical and scientific research, the environmental scan, and the Panel discussion on the topic and the conclusions drawn by the FIT Guidelines Expert Panel.

- **Section 3: *Methodology of the Guidelines Development and External Review Process*** This section summarizes the guidelines development process and the results of the formal external review by Ontario and international practitioners and colorectal cancer screening experts of the draft version of the FIT Guidelines and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the FIT Guidelines Expert Panel. The series is a convenient and up-to-date source of the best available evidence on three clinical issues related to FIT, developed through systematic review, expert consensus, evidence synthesis, and input from practitioners and CRC screening experts. Section 2 contains the systematic review of the evidence. The draft guidelines derived from the interpretation of that evidence and the expertise of the members of the Panel are detailed in Section 1. Sections 1 and 2 were circulated to health care providers, colorectal cancer screening experts and others in Ontario for their feedback. Section 3 present the feedback process results and any changes made to the draft document.

Internal Review: PEBC Director

Prior to the External Review (ER) of this EBS draft report, it was submitted for Internal Review on March 9, 2011 to the Director of the PEBC, Dr. Melissa Brouwers, a researcher with expertise in methodological issues. The document was approved, pending changes, by Dr. Brouwers on March 15, 2011. The key issues raised by the Director included the following:

1. Section One: Recommendations
   Some context should be provided. These are recommendations but the clinical questions are not recommendation inspired questions. Preface the recommendations with a statement of purpose, and then note the three clinical issues.
2. Section Two: Inclusion of guidelines.
   Please clarify the role of the guidelines that were obtained and discussed, detailing why no formal assessment of quality was performed.

In response to the Director's feedback, the following was added to the guideline:

1. Addition to Section One:
   Guideline Objective
   The purpose of this guideline is to evaluate the existing evidence concerning fecal immunochemical test (FIT) to inform the decision on how to replace the current guaiac fecal occult blood test (gFOBT) with a FIT in Ontario's ColonCancerCheck Program.

2. Where other guidelines were discussed in Section Two, the content has been modified. All the guidelines are noted when they are first mentioned (Section Two, page 6), and all appear in Table 11.

External Review: Targeted Peer Review (TPR)

Beginning on May 9, 2011, the PEBC Director-approved document was distributed to individuals in Canada with relevant expertise as part of the TPR process. It must be noted that the ER consisted of standardized survey questions that are used for all PEBC guidelines; therefore, some of the included questions regarding the recommendations are not fully relevant to this specific guideline. The survey was completed on June 20, 2011, and the results were analyzed. A total of seven individuals were invited to participate, and a total of seven submitted responses (100% response rate). Results are as follows:

1. Rate the guideline development methods							
Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	2	2	3	7	0
%	-	-	28.5	28.5	43	100	-
Comments: • Patient and pharmacist representation on the working group might have been useful. • It is not clear whether the RCTs included had concealment of allocation. • The included RCTs appear to have a major flaw in not clearly reporting their sample size calculations and hence could be reporting interim results.							
2. Rate the guideline presentation							
Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	1	4	2	7	0
%	-	-	14.5	57	28.5	100	-
Comments: • The guideline was well presented and organized with easy to find recommendations.							
3. Rate the guideline recommendations							
Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	1	3	2	6	1
%	-	-	14.5	43	28.5	85.5	14.5

Comments:
• The recommendations are sound; implementing a pilot program in Ontario is reasonable considering the evidence.
• In the pilot study, it might be useful to set two levels of cut-offs (75 and 100) and determine sensitivity, specificity, positivity, and PPV for each.
• Research questions for this pilot study might be:
  • Will capacity for colonoscopy influence the positivity rate?
  • Will the desired positivity rate influence the cut off value that will be used?							

4. Rate the completeness of reporting

Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	2	3	1	6	1
%	-	-	28.5	43	14.5	85.5	14.5

Comments:

- More information could have been provided regarding the successes and failures of the other provincial programs piloting FIT (e.g. participation rates, temperature stability issues).
- Some context for the E.U. guidelines might be useful to determine applicability in the Ontario setting, e.g. was the target of 1% rejection rate for kits based on a program that used bar-coded samples that were mailed?

5. Does this document provide sufficient information to inform your decision? If not, what areas are missing?

Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	2	3	2	7	0
%	-	-	28.5	43	28.5	100	-

Comments:

- The recommendation to implement a pilot study is reasonable considering the evidence available.
- Does the Expert Panel have a sense of how the capacity for colonoscopy will affect the success of the recommended pilot study?
- Information from some of the other provincial FIT programs would be useful in designing the Ontario pilot, e.g. program design characteristics, participation rates, confounding factors that may have an effect on their participation rates, how the lack of temperature stability of FIT samples was overcome.

6. What are the barriers or enablers to the implementation of this guideline report?

Barriers:

- Funding and resources for the pilot.
- There may be additional colonoscopy capacity needed within the province in order to run the pilot.

Enablers:

- Prospective participants are increasingly aware of the benefits, in terms of both health outcomes and cost-savings, of screening programs.
- Physicians would accept a more effective test.
- Community labs have expertise in provincial screening programs.

General questions:

7. Rate the overall quality of the guideline report

Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	0	0	1	2	4	7	0
%	-	-	14.5	28.5	57	100	-

8. I would make use of this guideline in my professional decisions

Response	1. Strongly disagree	2.	3.	4.	5. Strongly agree	TOTALS	Missing
N	0	0	1	2	3	6	1
%	-	-	14.5	28.5	43	85.5	14.5

9. I would recommend this guideline for use in practice

Response	1. Strongly disagree	2.	3.	4.	5. Strongly agree	TOTALS	Missing
N	0	0	1	2	3	6	1
%	-	-	14.5	28.5	43	85.5	14.5

Additional comments:

- The recommendations are sound; implementing a pilot program in Ontario is reasonable considering the evidence.

• Suggest determination of false positive rate and true positive rate at both lower (75) and higher (100) suggested cut off levels.

Expert Panel Response: Targeted Peer Review

Upon completion of the ER procedure, the Expert Panel reviewed the results of the TPR portion. The EBS was well received, and none of the TPR respondents rated the document as being of low quality or strongly disagreed with the findings. The majority of respondents rated the quality of the document high or highest and agreed with the findings. The Expert Panel had specific responses to the following comments:

- Regarding the investigation of various cut-off values, the Expert Panel believes that this is beyond the scope of the planned pilot study.
- Regarding the other provincial FIT programs, all available information regarding the experience and findings of the other provincial programs was obtained and reported on in this guideline.
- Regarding the E.U. guidelines, the 1% rejection rate was a target within a program that recommended use of procedures and tools that allow for the unambiguous identification of participants.
- Regarding the existing capacity for colonoscopy within the province, the Expert Panel believes that the province currently has adequate capacity to support the pilot study.

External Review: Professional Consultation (PC)

Beginning on May 9, 2011, the PEBC Director-approved document was distributed to individuals within the Province of Ontario with relevant expertise as part of a PC review process. It must be noted that the ER questions in the survey used for all PEBC guidelines are standardized; therefore, some of the included questions regarding the recommendations are not fully relevant to this specific guideline. The survey was completed on June 20, 2011 and the results were analyzed. A total of 262 individuals were invited to participate (a total of 253 received the survey to complete), and a total of 107 submitted responses (42.3% response rate). Results are as follows:

1. Rate the overall quality of the guideline report							
Response	1. Lowest quality	2.	3.	4.	5. Highest quality	TOTALS	Missing
N	1	12	22	51	19	105	2
%	0.95	11.4	20.9	48.5	18	98	1.8
2. I would make use of the guideline in my professional decisions							
Response	1. Strongly disagree	2.	3.	4.	5. Strongly agree	TOTALS	Missing
N	5	16	22	32	29	104	3
%	4.8	15.4	21	30.8	28	97	2.8
3. I would recommend this guideline for use in practice							
Response	1. Strongly disagree	2.	3.	4.	5. Strongly agree	TOTALS	Missing
N	10	15	27	26	24	102	5
%	9.8	14.7	26.4	25.5	23.5	95.3	4.7
4. What are the barriers or enablers to the implementation of this guideline report?							
Barriers:							
• The guideline offered no definitive recommendations regarding the use of FIT compared with gFOBT, although the recommendation to perform a pilot study, if implemented, will help to move practice forward.							

• If one of the goals of the ColonCancerCheck (CCC) program is to transition from gFOBT to FIT, then this review identified areas where FIT has limitations (especially with respect to stability with time and temperature) compared with gFOBT. • It will be difficult to implement a program unless these temperature and time stability issues are resolved. • As gFOBT is the current test, any change in practice will experience barriers. • The proportion of rural participants in Ontario will compound these time and temperature stability issues. • As colonoscopy is the definitive test, any decision between different FOBTs has to be framed with that in mind. • Many clinicians are limited in what they offer to patients by what the lab has available. • There will be an immediate increase in the kit costs in moving to FIT from gFOBT regardless of any possible long-term savings. • Family physicians will require some education on the new tests.
Enablers:
• The current CCC would make transitioning to any new test seamless. • The higher participation rates shown with most FITs are evidence of greater acceptance and compliance. • No dietary or medication restrictions should be more acceptable to participants. • Changing practice from gFOBT to FIT could improve colonoscopy wait times by increasing capacity. • There is a concern over the miss rates with gFOBT for CRC and polyps.
Additional comments:
• As piloting a FIT program would likely result in a greater number of colonoscopies performed, additional capacity needs to be implemented prior to the pilot starting for the geographical areas chosen. • Nurse Practitioners should be included in the Intended Users section, and involved in any pilot study.

Expert Panel Response: Professional Consultation

Upon completion of the ER procedure, the Expert Panel reviewed the results of the PC portion. Generally, the EBS was well-received although some respondents did rate the quality low or lowest and disagreed or strongly disagreed with the findings. However, the majority of the respondents did report the document being of good or high quality and agreed or strongly agreed with the findings. Regarding the comments received, the Expert Panel agrees with the majority of the feedback obtained and will take these comments into consideration moving forward. The Expert Panel agrees with the barriers and enablers identified in the External Review and will take them into consideration moving forward. The Expert Panel had specific responses to the following comments:

- As stated in response to a comment obtained during the TPR portion of the ER, the Expert Panel believes that the province currently has adequate capacity to support any increase in colonoscopy demand needed to support the pilot study.
- Regarding the comment about the inclusion of Nurse Practitioners, the Expert Panel agrees and the Intended Users statement was changed to "Primary Care Providers" to be more inclusive of the various clinicians to whom this document is intended.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario. It is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

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