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A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Guaiac Fecal Occult Blood Test (FOBT) Laboratory Standards

Report Date: November 26, 2007

An assessment conducted in January 2015 put Evidence-based Series (EBS) 15-4 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document (PEBC Assessment & Review Protocol)

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Section 1: Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series #15-4: Section 1

Guaiac Fecal Occult Blood Test (FOBT) Laboratory Standards: Recommendations

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The Guaiac FOBT Lab Standards Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

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Questions

1. **Guaiac Fecal Occult Blood Test (gFOBT) Performance Factors**
   What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value) of gFOBTs when used to detect colorectal cancer (CRC) (with either repeated gFOBT testing or after a single [one-time] test)?

2. **gFOBT Kit Usability Factors**

   - What gFOBT kit factors affect acceptability by users?
   - What is the effect of diet restrictions on gFOBT positivity?
   - What is the effect of medication use on gFOBT positivity?

3. **Laboratory Factors**
   What laboratory protocols are required to maximize the accuracy of a gFOBT kit in terms of:

   - Effect of temperature on specimen?
   - Time interval between specimen collection and laboratory processing?
   - Staff training?
   - Definition of a positive screening test?
   - Definition and resolution of an indeterminate result?

Recommendations

Based on the evidence in the published literature, information obtained from other colorectal cancer (CRC) screening programs, information obtained from unindexed literature available on the Web, kit manufacturers' instructions, and consensus, the Guaiac FOBT Lab Standards Panel has the following recommendations for Ontario's CRC Screening Program ("the Program"):

1. gFOBT Performance Standards

a) The Program should be initiated using one brand of gFOBT kit that is approved for sale by Health Canada to reduce variability in performance.

b) The gFOBT kit used in the Program should have:

i) Sensitivity for the detection of CRC on repeated testing: ≥ 40%

ii) Specificity for the detection of CRC on repeated testing: ≥ 95%.

c) The Program should develop a process to regularly monitor the gFOBT performance characteristics of participating laboratories.

2. gFOBT Kit Standards

a. The gFOBT kit should have three cards with two windows in each card.

b. The Program should not advise dietary restrictions except for citrus fruit and juices for the participants before or during the collection of stool samples for the gFOBT.

c. The Program should advise participants to discontinue vitamin C supplements and eliminate citrus fruit and juices for three days prior to and during collection of stool samples for the gFOBT.

d. The Program should not advise participants to discontinue oral intake of any prescribed medications, including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or iron, prior to or during the collection of samples for the gFOBT.

e. The Program should identify a gFOBT kit manufacturer that is willing to work with the Program to design a customized kit that includes:
   i. easy to read, understandable participant kit instructions to be included with all FOBT kits consistent with package insert;
   ii. the expiration date of the kit;
   iii. leak-proof envelope that meets Canada Post standards that would protect the sample during mailing, particularly in extreme temperatures; and
   iv. an outer envelope with easy-to-mail-back features such as the return address for a laboratory and pre-paid postage.

3. Laboratory Standards

a. Participating laboratories must be accredited by and ensure that all testing conforms to Ontario Laboratory Accreditation requirements.

b. The Program should use either one or a limited number of laboratories. The laboratories must have validated the selected gFOBT kit and must be performing sufficient gFOBTs to be proficient in the procedure.

c. The laboratory should develop an internal quality control protocol, and the laboratory must participate in the ongoing monitoring of their results.

d. The Program should develop and implement an external quality assurance program in which participating laboratories must enrol. This external quality assurance program

should be developed in collaboration with Ontario's Quality Management Program - Laboratory Services (QMP-LS) and be uniquely designed for the Program. All laboratories providing testing service to the Program must participate in this QMP-LS program as well as any other Program-defined monitoring and review of their results.

e. The contract with the participating laboratory(s) should include a requirement for an FOBT technical training program, including initial and ongoing training and the reassessment of the technologists reading the test results.

f. The stool sample card should have sufficient space for the participant to record his or her name and date of birth, as well as the date that the sample was obtained.

g. The laboratory should record and report the name of the participant, the date of birth, the date the last specimen was collected, the date the gFOBT kit was received at the lab, the date the kit was processed, and whether or not the kit received was beyond its expiration date.

h. Stool samples should not be processed earlier than two days (48 hours) from the date of collection.

i. The manufacturers' recommendations for the maximum time between specimen collection and laboratory processing should be followed.

j. A positive gFOBT is defined as one or more positive windows.

k. The laboratory should process the sample even if one or more of the windows do not contain a stool sample. An incomplete gFOBT is defined as one or more of the six windows not containing a stool sample and no positive window. If the kit is incomplete the laboratory should notify the primary care provider and the Program that the submitted kit was incomplete.

l. If the kit is not processable, the laboratory should send the participant a new kit with a letter explaining why the kit is being resent. As well, the laboratory should send notification to the primary care provider that a new kit has been sent.

m. An indeterminate gFOBT occurs when the test result cannot be established. When this occurs, the laboratory should send the participant a new kit with a letter explaining why the completion of another gFOBT is requested. The laboratory should also send notification to the primary care provider that a new kit has been sent.

n. The number of windows completed and the results for each card should be recorded by the laboratory and reported to the primary care physician and to the Program.

o. The Program should have processes in place to monitor laboratory performance according to these Standards. The Program or the monitoring body should have the ability to restrict non-proficient laboratories from testing the Program's FOBT specimens.

p. The Program should continually assess new evidence related to CRC screening methods.

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Evidence-Based Series #15-4: Section 2

Guaiac Fecal Occult Blood Test (FOBT) Laboratory Standards: Evidentiary Base

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INTRODUCTION

Colorectal cancer (CRC) is the most common cause of non–tobacco-related cancer deaths in Canadian men and women, accounting for almost 12% of all cancer deaths (1). In Ontario in 2007, an estimated 7,800 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 (1). 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) (2). Screening with the FOBT decreases CRC mortality and is associated with an increase in the proportion of detected cancers that are Dukes' Stage A (3-5). In 1999, Cancer Care Ontario convened an expert panel to develop recommendations for a CRC screening program in Ontario. The panel recommended a province-wide FOBT-based CRC screening program for average-risk individuals 50 to 74 years of age (6). In 2002, this recommendation was echoed at the national level by a committee convened by Health Canada (7).

A one-year pilot study to evaluate recruitment strategies for FOBT screening was funded by the Ministry of Health and Long-Term Care (MOHLTC) in June 2003 (8). In June 2005, CCO submitted its proposal to the MOHLTC for a provincial population-based CRC screening program using FOBT.

CCO and the MOHLTC jointly announced a population-based CRC screening program for Ontario in January 2007. The program will use FOBT for screening those at average risk and will use colonoscopy as the initial screening test for those at increased risk because of having a history of one or more first-degree relatives diagnosed with CRC. Colonoscopy will also be used to investigate the approximately 2-3% of screenees who will have a positive FOBT. Colonoscopy Standards were developed by CCO's Program in Evidence-Based Care (PEBC) to support the Ontario CRC Screening Program (9).

This document describes the findings and recommendations of CCO's Guaiac FOBT Lab Standards Panel (please see Appendix A). This Panel was convened in October 2006 by the PEBC to evaluate the evidence concerning existing guaiac FOBT kits and, based on this evidence, to develop guaiac FOBT Standards for the Ontario CRC Screening Program.

The FOBT is an indirect test for the presence of CRC, and individuals with a positive test are advised to undergo a colonoscopy to determine whether CRC is present. There are two types of FOBT kits available, the guaiac FOBT (gFOBT) kit and the immunochemical FOBT (iFOBT kit). The focus of this document is on the gFOBT, which will be used by the Ontario CRC Screening Program at the outset. The gFOBT detects blood in the stool which may be due to bleeding from CRC. To complete an FOBT, participants are required to apply six fecal samples (two samples from each of three consecutive spontaneously passed stools) onto test areas (windows) on FOBT kits (cards). The test is based on the oxidation of guaiac (impregnated on the card) by hydrogen peroxide catalyzed by the peroxidase activity of hemoglobin. gFOBTs are not specific for human hemoglobin. Although there are many brands of gFOBT kits available, the focus of this document is on the following five gFOBTs that are currently approved for sale in Canada (Level 2 approval, Health Canada): Hemoccult II, Hemoccult II SENSA, ColoScreen, TRI-SLIDE, and Hema Screen.

The purpose of this document is to evaluate existing evidence concerning the following three key aspects of gFOBT kit use:

1. **gFOBT Performance Factors**
   What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value) of gFOBTs when used to detect CRC (with either repeated gFOBT testing or after a single [one-time] test)?

2. **gFOBT Kit Usability Factors**
   While there are many issues affecting participation in a FOBT-based CRC screening program, the focus of this review is on the factors pertaining to the gFOBT kits that may affect either the acceptability of the kits by users or the test results.

   - What gFOBT kit factors affect acceptability by users?
   - What is the effect of diet restrictions on gFOBT positivity?
   - What is the effect of medication use on gFOBT positivity?

3. **Laboratory Factors**
   What laboratory protocols are required to maximize the accuracy of a gFOBT kit in terms of:

   - Effect of temperature on specimen?
   - Time interval between specimen collection and laboratory processing?
   - Staff training?
   - Definition of a positive screening test?
   - Definition and resolution of an indeterminate result?

METHODS: SEARCH STRATEGIES

Literature Search

The MEDLINE, EMBASE, and CINAHL databases and the Cochrane Library database of Systematic Reviews were systematically searched in January and February 2007 for articles assessing gFOBT screening for CRC published between January 1966 and February 2007. Search terms included “screening” “fecal”, “faecal”, “guaiac”, “occult”, “FOBT“, “diet“, “medication”, “aspirin”, “NSAIDS”, “iron”, and “colorectal neoplasia”. Review articles published between these dates were retrieved, and their reference sections were used to cross-reference the MEDLINE search. Panel members were also canvassed to ensure that no relevant articles were missed.

Inclusion Criteria

Eligible sources of information included:

1. Published full reports with information on any of the three key aspects outlined above.
2. Randomized controlled trials (RCTs), retrospective study designs, prospective study designs, and mixed designs.
3. Reports published in English.

Exclusion Criteria

1. Studies that included symptomatic participants.

CRC Screening Program Environmental Scan

Five countries have organized CRC screening programs that use gFOBT: the United Kingdom (UK), Israel, Finland, France, and Denmark. Representatives from these programs were contacted and asked the following questions: 1) which gFOBT was chosen by the program; 2) what was the reason(s) for this choice; 3) what dietary and medication restrictions are required by participants; and 4) what protocols are in place for storage, processing, and reporting of indeterminate results?

Internet Search

An Internet search was conducted to capture the relevant unindexed literature not identified by the literature search described above. The intent was to obtain government and nongovernment publications, policy statements, health technology assessments, and CRC screening protocols of other jurisdictions. In addition, members of the Panel were canvassed regarding additional unindexed documents. An Internet search using the Google™ search engine (www.google.ca) was performed on March 2 and 5, 2007, using the terms “FOBT,” “colorectal screening,” and “occult blood test.” The Internet search strategy consisted of a review of the first 50 hits, and if no compelling sources were flagged in hits 40 through 50, the search strategy was considered complete. If relevant sources continued to be found, the search continued until a series of 10 non-useful hits had been reviewed.

Inclusion Criteria

Eligible sources of information included any report that provided information on the three key aspects of gFOBT information outlined above.

Information Provided in Test Kit Instructions

The instructions from test kits licensed for use in Canada were obtained, and the relevant information was reviewed. In Ontario, Hemoccult II (10) and Hemoccult II SENSA (11) are distributed by Beckman Coulter Inc., ColoScreen (12) is distributed by Helena Laboratories, TRI-SLIDE (13) is distributed by Cenogenics Corp., and Hema Screen (14) is distributed by Immunostics, Inc.

METHODS: DEFINITIONS

Table 1. Relationship between screening test result and presence of cancer.

	Cancer Present	
Screening Test Result	Yes	No
Positive	a	b
Negative	c	d

Definitions (see Table 1)

- True positive: those with a positive screening test and confirmed cancer (a),
- False positive: those with a positive screening test and no confirmed cancer (b),
- True negative: those with a negative screening test and no confirmed cancer (d),
- False negative: 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)

RESULTS: DATA SOURCES IDENTIFIED

Literature Search Results (Table 2)

Of 356 articles identified in the literature search, 126 were deemed relevant for a full article review. Of these, 40 articles (one guideline, one meta-analysis, five RCTs, 32 prospective studies, and one retrospective study) met the inclusion criteria and were retained.

CRC Screening Program Environmental Scan Results

The National Health Service (NHS) Bowel Screening Program (UK), the Finnish Cancer Registry, and the National Israeli Breast and Colorectal Cancer Detection Program responded to the environmental scan questions and provided information about their CRC screening programs.

Internet Search Results

Nine sources were deemed relevant by a title review and were obtained for full review. The five that met the inclusion criteria were retained and are described below (2,8,15-17).

- **The Centre for Reviews and Dissemination: Diagnostic Accuracy and Cost-Effectiveness of FOBT Used in Screening for CRC: A Systematic Review, February 2007 (17).** The Centre for Reviews and Dissemination (CRD) is a facility commissioned by the NHS Research and Development Division (UK) to identify and review the results of good-quality health research and to disseminate the findings to key decision makers in the NHS and to consumers of health care services. This systematic review sought to determine the diagnostic accuracy and cost-effectiveness of four types of gFOBT kits, two of which are available in Ontario (Hemoccult II and Hemoccult II SENSA), for CRC screening in an average-risk population. The CRD also attempted to identify which gFOBT was the most accurate and cost-effective.

- **The Ontario Fecal Occult Blood Test (FOBT) Pilot Project; CCO and the MOHLTC, in collaboration with the Institute for Clinical Evaluative Sciences (ICES), and the Ontario Association of Medical Laboratories (OAML), March 2006 (8) .** Results from this pilot project were used to establish protocols for the Ontario CRC Screening Program. The pilot project compared the uptake of completed kits, using two methods of promotion and recruitment for FOBT screening in average-risk men and women. These methods were through either primary care physicians or local public health units. The project also assessed the knowledge, attitudes, and screening behaviours of the public, physicians, and public health unit staff through surveys, focus groups, and key-informant interviews.

  The quasi-randomized design used an intervention period of 15 months (March 2004 to May 2005) and was piloted in 12 randomly selected public health unit regions (out of the 37 in Ontario). Primary care physicians distributed the gFOBT kits in six regions, and, in the other six regions, the local public health units distributed the kits using strategies they deemed feasible and appropriate for their communities.

- **NHS Purchasing and Supply Agency, Centre for Evidence-Based Purchasing (CEP); Four Faecal Occult Blood Testing Kits Evaluation Report, January 2006 (15).** The Guildford Medical Device Evaluation Centre (UK) completed an evaluation of four gFOBT kits, three of which are available in Ontario (Hema Screen, Hemoccult II, and Hemoccult II SENSA), to provide independent and objective evaluations. To be evaluated, the kits had to meet the following requirements, as dictated by the NHS screening program: Conformité Européene (CE) marking; card collection device; single-step analysis; minimum 14-day sample stability on the card; suitable for posting in the UK, both to and from the participants; manufacturer willing to customize the kits to the Program's requirements; positive and negative quality control system associated with each fecal sample; and clinical performance comparable to the kit used in the pilot study (Hema Screen) or offer improvements in both specificity and sensitivity. The kits were subjected to a laboratory assessment of the analytical sensitivity (i.e., the fecal haemoglobin concentration that is the threshold for detection) and sample stability. The packaging and instructions for use and the supplier's training scheme were assessed, along with the ease of use and time needed to process each test. The observations made by the evaluation team were supplemented by comments from users, selected from a list provided by the supplier.

- **Canadian Task Force on Preventive Health Care Screening Strategies for Colorectal Cancer: Systematic Review & Recommendations; Technical Report, February 2001 (2)** This systematic review was conducted to evaluate the evidence and to make recommendations on the effectiveness of specific screening techniques for CRC in asymptomatic patients of average risk and above-average risk.

- **Medical Devices Agency (MDA) Evaluation Report: Evaluation of Eleven Faecal Occult Blood Test Kits, March 2000 (16).** The MDA Evaluation Centre in the UK evaluated 11 gFOBT kits to assess their analytical sensitivity, reliability, and ease of use. Three kits that were evaluated are currently approved for sale in Ontario (Hema Screen, Hemoccult II, and Hemoccult II SENSA).

Information Provided in Test Kit Instructions Results

Information and recommendations from manufacturers of gFOBT kits available in Canada was provided for Hemoccult II (10), Hemoccult II SENSA (11), ColoScreen (12), TRI-SLIDE (13), and Hema Screen (14).

Table 2. Summary of literature used for each key aspect of gFOBT kit use.

Key Aspect	Guideline	Meta-analysis	Randomized Controlled Trials	Prospective Studies	Retrospective Studies	Reports	CRC Programs	Test Kit Instructions
Performance Factors	0	0	4	17	0	4	0	0
Usability Factors	0	1	1	12	0	3	3	5
Laboratory Factors	1	1	0	4	1	1	3	5

RESULTS: EVIDENCE CONCERNING THE THREE KEY ASPECTS OF gFOBT KIT USE

1. gFOBT Performance Factors: What are the performance characteristics (sensitivity, specificity, positivity, and positive predictive value) of gFOBTs when used to detect CRC (with either repeated gFOBT testing or after a single [one-time] test)?

Literature Search Results

The published gFOBT performance characteristics examined included test sensitivity and specificity for the detection of CRC, test positivity and the positive predictive value for CRC (PPV). Sensitivity, specificity, and PPV were estimated in most studies (3-5,18-32) because not all participants were offered colonoscopies. In these studies, only those participants with a positive gFOBT were offered any follow-up evaluation. Therefore, the number of false negatives could not be calculated because those participants with a negative FOBT could not have their test results confirmed with a colonoscopy.

Repeated Testing

The literature search identified six studies that measured the performance of gFOBT with repeated annual or biennial testing (3-5,22,24,25,28,30) (Table 3). The purpose of these studies was to compare the CRC mortality rate among those people who were screened for CRC with those who were not screened. Five of the screening studies used the Hemoccult II kit (3-5,22,24,25,28). All samples were rehydrated in one study (25), and 82.5% of the samples were rehydrated in another (5); samples were not rehydrated in the remaining studies. One study used Hemoccult II SENSA (30). Hemoccult II SENSA is similar to Hemoccult II but has a different developer fluid formulation that allows the detection of lower levels of hemoglobin. Participation rates for completing at least one gFOBT ranged from 52.8% to 78.4%.

The test positivity for Hemoccult II in non-rehydrated samples varied from 0.8% to 2.4% and for rehydrated samples, from 4.4% to 9.8%. Test positivity for Hemoccult II SENSA was 4.7% in one study.

Two approaches were used to define sensitivity. Five studies (3,4,22,24,25,28,30) used the following approach: sensitivity = true positives/(true positives + false negatives), where, for a true positive, the FOBT detects the cancer and, for a false negative, those with a negative screen had a CRC detected between screening rounds or during follow-up after the last screening round. In the studies that used this approach, the sensitivity of Hemoccult II for the detection of CRC ranged from 51.1% to 72.7% and for Hemoccult II SENSA, ranged from 69.2% to 100%. For Hemoccult II rehydrated tests, the sensitivity for the detection of CRC was 81%. The specificity of Hemoccult II for the detection of CRC was 97.7% in one study. The specificity of rehydrated Hemoccult II was 90.4% in one study. The specificity of Hemoccult II SENSA varied from 95.5% to 97%. The PPV for Hemoccult II ranged from 8.0% to 17.0%, and for rehydrated Hemoccult II, the PPV ranged from 4.4 to 5.1%. For Hemoccult II SENSA, PPV ranged from 2.4% to 5.5%.

The sixth study used a different approach to define sensitivity (5). In this study, the cancers diagnosed in the first year after screening were included in the calculation as follows: sensitivity = true positives/(true positives [CRC discovered within one year after a positive FOBT] + false negatives [CRC discovered within one year after a negative FOBT]). The sensitivity and specificity for detecting CRC for annual and biennial screening in this study were 80.8% and 92.2% for sensitivity, and 97.7% and 90.4% for specificity, respectively. The PPVs for annual and biennial screening were 5.6% and 2.2%, respectively.

The Canadian Task Force on Preventive Health Care (CTFPHC) recalculated the sensitivity for the sixth study (5). When sensitivity was calculated as the number of cancers detected through screening divided by the total number of cancers, the results were 49.5% for annual and 38.3% for biennial Hemoccult II testing (specimens were rehydrated prior to testing). In addition, for one of the five other studies that did not report test sensitivity (4), the CTFPHC calculated a sensitivity of 48% for biennial testing.

Single Test

Thirteen prospective studies were identified that provided data on performance characteristics for gFOBT in a single application in an asymptomatic population (18-21,23,26,27,29,31-35). Most studies compared a gFOBT with either an iFOBT or another gFOBT. Only the results for the gFOBTs are reported in Table 4. Unless otherwise stated, all studies used unrehydrated samples; only three studies (21,27,34) rehydrated the Hemoccult II samples. Among these 13 studies, the UK pilot study used the Hema Screen kit (32), while the remainder of the studies used Hemoccult II (18-21,23,27,29,31,33-35) or Hemoccult II Sensa (26) or both (19,21,27,29).

Test positivity for Hemoccult II varied from 1.1% to 20% and for rehydrated samples from 5.4% to 8.3%. Test positivity for Hemoccult II SENSA ranged from 4.8% to 15%. In all studies, participants with a positive gFOBT were offered follow-up evaluation, which in most studies was colonoscopy. However, most studies (10 of 13) did not offer follow-up evaluation for those with a negative gFOBT, and therefore sensitivity could only be estimated.

In three studies, (33-35), colonoscopies were performed on all subjects (i.e., with both FOBT positive and negative results), resulting in a more accurate determination of sensitivity and specificity. In one study that used rehydrated samples, the sensitivity for the detection of CRC was 50%, and the PPV was 6.5% (34). The other two studies reported sensitivities of 12.9% and 25% and specificities of 95.2% and 80%, respectively (33,35).

For the other ten studies, the estimated sensitivity of Hemoccult II for detecting CRC ranged from 25% to 37.1%. The sensitivity of Hemoccult II SENSA for detecting CRC ranged from 71.7% to 79.4%. Of the two studies (21,27) that rehydrated the samples, only one reported sensitivity, which was 85.7% (21). The specificity for detecting CRC using unrehydrated samples ranged from 97.6% to 99.6%. The studies that used rehydrated Hemoccult II samples (21,27) did not report specificity. The PPV for Hemoccult II ranged from 4.2% to 7.9% and for rehydrated Hemoccult II, the range was 2.6% to 7.7%. The one reported specificity for Hemoccult II SENSA was 86.7%, and the PPV ranged from 2.5 % to 14%. The PPV for Hema Screen was 10.9% (32).

CRC Screening Program Environmental Scan Results

No additional information was obtained.

Internet Search Results

The CRD conducted a systematic review of the diagnostic accuracy of four gFOBTs, two of which are available in Ontario, (Hemoccult II and Hemoccult II SENSA). They concluded that there was little evidence that any particular gFOBT reviewed was superior in performance to any other (17).

The Ontario FOBT Pilot Project, a province-wide pilot project that used two gFOBT kits (Hemoccult II and Hema Screen), was performed by three commercial medical laboratories (MDS, Gamma-Dynacare, CML) (8). Six thousand nine hundred seventy-two (6,972) individuals completed an FOBT kit, with an overall positivity rate of 2.8%. However, there were differences in the positivity rates across regions, in part due to differences in the kits used and also perhaps due to the criteria used by the laboratories to define a positive test result. The one laboratory that reported a higher positivity rate (5.4%) used testing procedures that differed slightly from those of the other two. Another laboratory had a higher proportion of tests deemed unsuitable for interpretation (3.5% compared with the mean of 1.2%).

The MDA evaluation of gFOBTs concluded that there was no clear evidence that one particular gFOBT reviewed was superior in performance to any other (16).

Information Provided in Test Kit Instructions Results

No additional relevant information was found in the test kit instructions (package inserts in the Health Canada-approved gFOBT kits). All studies referenced in the test kit package inserts are included in Tables 3 and 4.

Table 3. Test characteristics for the detection of colorectal cancer using gFOBT in repeated testing.

Study	Study Design	Study Population	Follow-up	Reference Standard	FOBT type	Screening round	Participation (%)	Pos (%)	Sens (%)	Spec (%)	PPV (%)
Burgundy, France Faivre et al, 2005 (22); Jouve et al, 2001 (24)	Case-control, Biennial	45,603 aged 45-74	11 years	Colonoscopy for a positive FOBT and follow-up	Hemoccult II (unrehydrated)	1 2 3 4 5 6	52.8 54.0 57.3 58.3 56.2 53.8 Mean: 55.3	2.1 1.3 1.5 1.2 1.3 1.4 Mean: 1.4	72.7 51.1 55.9 69.4 56.9 NR Mean: 61	NR	9.8 8.2 12.8 14.7 13.0 12.7 Mean: 11.5
Israel Rennert et al, 2001 (30)	Pro-spective	22,193 aged 50-74	3 years	Results of follow-up tests from primary care physician	Hemoccult II SENSA	1 2 3	NR	4.7 NR NR	85.3 69.2 100.0	95.5 96.6 97.0	5.5 2.4 4.1
Funen, Denmark Kronborg et al, 1996 (4)	RCT, Biennial	30,967 aged 45-75	10 years	Colonoscopy for a positive FOBT or DCBE and follow-up	Hemoccult II (unrehydrated)	1 2 3 4 5	67 93 [A] 94 [A] 94 [A] 92 [A]	1.0 0.8 0.9 1.3 1.8	NR	NR	17 8 16 11 10
Nottingham,UK Hardcastle et al, 1996 (3); Moss et al, 1999 (28)	RCT, Biennial	76,466 aged 45-74	10 years	Colonoscopy for a positive FOBT and follow-up	Hemoccult II (unrehydrated)	1 2	59.6 (at least 1 screening test)	2.1 1.2	54.1	NR	9.9 11.9
Goteburg, Sweden Kewenter et al, 1994 (25)	RCT	68,308 aged 60-73	7 years	Positive FOBT offered DRE, PS, RS, DCBE and follow-up	Hemoccult II (All rehydrated)	1 2	63 60	4.4 5.1	81	NR	4.4 5.1
Minnesota, USA Mandel et al, 1993 (5)	RCT, annual, biennial	46,551 aged 50-80	13 years	Colonoscopy or DCBE or FS for a positive FOBT and follow-up	Hemoccult II (unrehydrated) Hemoccult II (82.5% rehydrated)	NR	75.2% participated in annual screening and 78.4% in biennial	2.4 9.8	80.8 92.2	97.7 90.4	5.6 2.2

A Figures were calculated using the percentage of those who participated in the previous round (were alive and without CRC or adenomas detected) since only they were invited to participate in the next round (percentage of original participants: for rounds 2, 3, 4, and 5: 61%, 56%, 51.5%, and 46%)

Abbreviations: Pos-Positivity; Sens–Sensitivity; Spec-Specificity; PPV–Positive Predictive Value; NR–Not Reported; RCT–Randomized Controlled Trial; DCBE–Double Contrast Barium Enema; DRE–Digital Rectal Exam; PS–Proctoscopy; RS–Rectosigmoidoscopy; FS–Flexible Sigmoidoscopy

Table 4. Test characteristics for the detection of colorectal cancer using gFOBT in single (one-time) testing in asymptomatic populations.

Study	Study Design	Study Population	Reference Standard	FOBT type	Pos (%)	Sens (%)	Spec (%)	PPV (%)
Imperiale et al, 2004 (33)	Prospective	4404 asymptomatic age ≥50 yr	Colonoscopy	Hemoccult II (unrehydrated)	10.8	12.9	95.2	5.5
Sung et al, 2003 (35)	Prospective	505 asymptomatic age ≥50 yr	Colonoscopy	Hemoccult II (unrehydrated)	20	25	80	1.0
Lieberman and Weiss, 2001 (34)	Prospective	2885 asymptomatic age 50-75 yr	Colonoscopy	Hemoccult II (rehydrated)	8.3	50	NR	6.5
Guittet et al, 2007 (23)	Prospective	10,804 age 50-74 yr	Colonoscopy for a positive FOBT	Hemoccult II (unrehydrated)	2.4	NR	NR	7.3
UK CRC Screening Pilot Group, 2004 (32)	Prospective	271,646 age 50-69 yr	Colonoscopy for a positive FOBT	Hema Screen (unrehydrated)	1.9	NR	NR	10.9
Ko et al, 2003 (26)	Prospective	2964 participants [A]; mean age 65.4 yr	Colonoscopy or DCBE for a positive FOBT	Hemoccult II SENSA	9.0	NR	NR	14
Levin et al, 1997 (27)	Prospective	8293 asymptomatic age ≥ 50 yr	Follow-up with physician	Hemoccult II (unrehydrated)	5	NR	NR	5.4
				Hemoccult II (rehydrated)	7	NR	NR	2.6
				Hemoccult II SENSA	15	NR	NR	4.9
Allison et al, 1996 (19)	Prospective	10,702 asymptomatic age ≥ 50 yr	Colonoscopy or 2 yr follow-up FS or 2 yr follow-up	Hemoccult II (unrehydrated)	2.5	37.1	97.7	6.6
				Hemoccult II SENSA	13.6	79.4	86.7	2.5
Castiglione et al, 1994 (21)	Prospective	1509 asymptomatic; mean age 55 yr	Colonoscopy or DCBE for a positive FOBT	Hemoccult II (rehydrated)	5.4	85.7	NR	7.7
				Hemoccult II SENSA	4.8	71.7	NR	7.2
Petrelli et al, 1994 (29)	Prospective	39,000 from general population; mean age 56.6 yr	Follow-up with physician for those with a positive FOBT	Hemoccult II (unrehydrated)	5.1	NR	NR	5.4
				Hemoccult II SENSA	9.5	NR	NR	3.6
Robinson et al, 1994 (31)	Prospective	1489 asymptomatic age 50-75 yr	Colonoscopy for a positive FOBT	Hemoccult II (unrehydrated)	1.1	NR	99.6	5.9
Ahlquist et al, 1993 (18)	Prospective	12,312 relatives of CRC patients age ≥ 50 yr	Colonoscopy for a positive FOBT	Hemoccult II (unrehydrated)	3.8	25	NR	4.2

Bang et al, 1986 (20)	Prospective	1473 asymptomatic males age ≥20 yr	FS, Colonoscopy for a positive FOBT	Hemoccult II (unrehydrated)	2.6	25	97.6	7.9

A Some participants may have been had signs or symptoms related to the lower gastrointestinal tract
Abbreviations: FS–Flexible Sigmoidoscopy; Pos–Positivity; Sens–Sensitivity; Spec–Specificity; PPV–Positive Predictive Value; NR–Not Reported

2. gFOBT Kit Usability Factors

What gFOBT kit factors affect acceptability by users?

Literature Search Results

One study (36) asked 50 adults to collect Hemoccult gFOBT specimens using three different specimen collection and application methods (a wooden stick, toilet tissue smear, and direct smear), and rank their preferred method. The wooden stick and toilet tissue smear methods were the most preferred (51% and 46%), and subjects stated that they would be more likely to return the kit if they were able to choose the method of specimen collection.

CRC Screening Program Environmental Scan Results

The approaches used in other jurisdictions to identify a suitable kit to be used in their CRC Screening Programs provided additional information on other aspects of kit acceptability. The results are summarized below (Table 5).

Table 5. CRC screening program environmental scan results for gFOBT kit usability factors.

CRC Screening Program	FOBT test	Usability Factors Influencing the Choice of Kit by the Program
NHS Bowel Screening Program	Hema Screen	See details below under Internet Search Results (Table 6).
Finnish Cancer Registry	Hemoccult II	The Hemoccult II was deemed easy to mail and feasible to use. The test cards were very clear and big enough for stickers to be attached (each kit was labelled before it is sent, to identify participant identity and when it was sent), there was little written text in the test card, and clear marks on where to open the card.

Internet Search Results

The analysis done by the CRD, using four gFOBT kits, concluded that no gFOBT kit was superior to any other in terms of performance and that factors other than accuracy should be considered when deciding which gFOBT to use in a CRC screening program (17). The factors included the effects of the stool sampling methods and dietary and medication restrictions upon compliance; the logistics of storing, obtaining, and returning the gFOBT kit; cost-effectiveness; and the lack of immediate results for the participant. However, data included in the report provided no evidence pertaining to any of these factors.

The NHS CEP report evaluated four gFOBT kits (15), examining analytical sensitivity and sample stability. The packaging and instructions for use and the supplier's training programs were assessed, along with ease of use and time required to process each test. Observations made by the evaluation team were supplemented with comments from the users, (selected from a list provided by the manufacturer). The results are presented below (Table 6). Additional laboratory specific results are also presented in Appendix B.

Table 6: Results from NHS CEP evaluation of gFOBT kit usability factors (15).

FOBT Test	Sample collection Spatula	Sample Windows	CEP and User's Comments
Hemoccult	Pointed cardboard spatula, very easy to sample and spread. Flushable.	2 rectangular, size matches spatula edge, so easy sample application	• The sample windows are rectangular and slightly wider than the spreading edge of the sample applicator, which makes it easy to spread the sample evenly across the guaiac paper and not onto the surrounding card. • The patient instructions specify a pea-sized sample of stool is to be used to cover the sample area, which guides the required sample size.
ColoScreen	3 wooden sampling sticks, sturdy, easy to sample but rounded end makes spreading uneven. Not flushable.	2 rectangular	• The triple card is fully perforated between the sections and users might separate the sections, making the cards more difficult to handle in the laboratory. • All users (5/5) state that the envelope was easy to open and that they did not observe any leakage of sample from it. • Some patients had difficulty interpreting the loading instructions. • Users (6/6) stated that it was easy to deliver the required amount of developer and that the colour development was generally good and easy to read, although 3/6 added that weak positives were not so easy.
Hema Screen	Tapered cardboard spatula, rather short, easy to sample and spread. Flushable.	2 oval, smaller than others	• The customized triple card is not perforated between the three sections, ensuring that each participant's samples arrive as a single entity. • Users (4/4) found the envelope easy to open. • The instructions specify "a very thin smear," and this is open to wide interpretation and is likely to lead to variability in the sample size. • Users found it easy to add the correct amount of developer and all (6/6) stated the results were relatively easy to read, although 4/6 admitted some difficulty with weak positives.
Note: Analytical sensitivity is susceptible to loading levels (amount of sample on card). All cards were loaded according to the instructions for use but only Hemoccult defined this well. The smaller windows on the Hema Screen card allow application of fewer samples.			

The MDA Evaluation Report on 11 FOBT kits involved two field studies that assessed stool collection systems and patient preference (16). The first study was conducted using thirty volunteers recruited by the Colo-Rectal Cancer Understanding and Screening Trust (CROCUS). The volunteers were asked to allocate scores from 1 to 5 to each of eight questions concerning the use of the kit, and to make subjective comments on good and poor features.

The results showed a preference for a tube device (specimen placed into a glass test tube) over a card or a wipe (a sample collection method in which one uses the kit wipe after defecation; removes the perforated top layer of the wipe, leaving dots of sample on an inner layer of guaiac-impregnated paper; and then folds the adhesive-edged waterproof outer layer to seal the sample inside). The tube was found to be the least messy—it was easier to apply the correct amount of sample and close the container. The card was ranked second overall; it was particularly easy to collect the correct amount of sample and label and close the card but was messy. The wipe was the least popular, although it had the advantage of not requiring a separate collection of the sample. However, the sample was messy to collect, and it was difficult to close and label the kit.

The second MDA study, by the Guildford Undetected Tumour Survey (GUTS), involved three stool collection systems. Forty participants were asked to rate the systems by responding to five questions, and the results showed little difference in the overall ease of use for any particular kit. Each system had advantages and disadvantages. In one system, a longer wooden stick reduced the risk of the participants contaminating their fingers but was not flushable, unlike the shorter stick. A tube and bottle sample was less messy than a card sample but more difficult to close, and the card was easier to mail.

Information Provided in Test Kit Instructions Results

The Hemoccult II, Hemoccult II SENSA, ColoScreen, and Hema Screen instructions did not provide any information regarding how kit factors might affect usability.

Cenogenics (TRI-SLIDE) stated that, to aid in the use of the gFOBT, they had provided large writing spaces for labelling and had tried to make the patient instructions easy to understand. As well, they placed the word “occult” on the product in an attempt to improve patient understanding of the product’s purpose. The TRI-SLIDE FOBT has a wooden applicator stick for sample collection and two small rectangular sample windows. Patients are asked to apply a thin layer inside the test window. There are also spots for positive and negative controls.

The Hemoccult II SENSA sample collection information is the same as the Hemoccult II (See Table 6 above).

What is the effect of diet restrictions on gFOBT positivity?

Literature Search Results

One meta-analysis and two studies compared gFOBT positivity rates in participants who completed a gFOBT with or without dietary restrictions. Pignone et al (37) conducted a meta-analysis of four randomized and one quasi-randomized study that randomized or assigned patients to either a “dietary restrictions” or a “no dietary restrictions” arm before completing a Hemoccult FOBT. The dietary restrictions varied in duration (24 or 48 hours before testing or only during testing) and in the foods that were restricted. However, all the dietary restrictions included no red meat (four studies restricted red meat before and during testing, while one restricted it during testing only). Four of the studies restricted certain vegetables before and during testing, and two of the studies restricted vitamin C and aspirin. No study found a statistically significant difference in gFOBT positivity rates between any of the groups. As well, the meta-analysis showed no difference in the summary positivity rate between those assigned to dietary restriction versus those not restricted. The advice given to participants to restrict their diets did not substantially reduce the completion of the gFOBT kits except in one study where the dietary restriction was more extensive.

Rozen et al (38) conducted a prospective study in a screening program that used Hemoccult II SENSA over two phases in an Israeli population, who typically have a low intake of red meat. In phase one, 403 participants were instructed to eat a low peroxidase-containing diet for three days before and during specimen collection (three or more days) and to discontinue medications such as aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and vitamin C one week before starting the stool collection. In phase two, 541 participants were given no dietary recommendations but were asked not to take vitamin C supplements. Test development was delayed three to 14 days after sample collection. In neoplasia-free screenees, there was no statistically significant difference in Hemoccult II SENSA positivity with or without dietary restrictions (7.2% for diet restricted versus 5.5% for no restrictions) if development was delayed three or more days after the last sample was collected. The authors concluded that delaying development of Hemoccult SENSA kits by three to 14 days allows the breakdown of ingested peroxidases. They also concluded that, when using Hemoccult II SENSA kits, dietary restrictions are not necessary in populations that do not consume large amounts of red meat.

Sinatra et al (39) conducted a study in 61 healthy volunteers, (mean age, 26 years) comparing two diets and varying times to development, using Hemoccult and Hemoccult II SENSA. Diet A (low heme/low plant peroxidase) and Diet B (low heme/high plant peroxidase) commenced three days before the sample collection began and continued until the collections were completed. The volunteers completed test cards—noting the day and time of passage—for each of three consecutive stools. Diet A specimens (one sample test card with two windows per gFOBT per stool) were developed 24 hours after collection. Diet B specimens (three test cards consisting of six windows per gFOBT per stool) were developed 24, 48, and 72 hours after collection. The study found that gFOBT positivity rates decreased rapidly as the time between sample collection and development increased. The authors concluded that a peroxidase-rich diet does not need to be avoided when using Hemoccult and Hemoccult SENSA if the development is delayed for at least 48 hours after sample collection.

CRC Screening Program Environmental Scan Results

The results are presented below (Table 7).

Table 7. CRC screening program environmental scan results for diet restrictions.

CRC Screening Program	**gFOBT test**	**Diet Restrictions Being Used**
NHS Bowel Screening Program	Hema Screen	No diet restrictions. However, dietary restrictions may be requested prior to completion of a second test if it is felt that the positive result was due to diet.
Finnish Cancer Registry	Hemoccult II	Intake of raw meat, blood, and liver is restricted 3 days before and during testing. Otherwise, the diet is unrestricted.
National Israeli Breast and Colorectal Cancer Detection Program	Hemoccult II SENSA	No diet restrictions.

Internet Search Results

No relevant information was found concerning gFOBT diet restrictions.

Information Provided in Test Kit Instructions Results

The instructions for diet restrictions for the gFOBT kits approved for sale in Canada are tabulated below (Table 8).

Table 8. Diet restriction recommendations from manufacturers of gFOBT kits available in Canada.

FOBT	Test Kit Information
Hemoccult II	Avoid red meats (beef, lamb) and liver for three days before and during stool collection
Hemoccult II SENSA	Avoid red meats (beef, lamb) and liver for three days before and during stool collection
ColoScreen	To be avoided: (a) Meat: diet should not include any red or rare meat; (b) Raw fruits and vegetables containing high peroxidase activity: turnip, broccoli, cauliflower, red radishes, cantaloupe, horseradish, parsnip
TRI-SLIDE	Foods that should be avoided two days prior and continuing through the test period are: Meat: rare cooked meats such as beef; Raw vegetables: turnips, horseradish, radishes, broccoli, carrots, cauliflowers, mushrooms and cucumbers, (cooking the raw vegetables listed for 20 minutes will destroy their peroxidase activity); Fruits: cantaloupes and grapefruit
Hema Screen	A red-meat-free, high residue diet is recommended, starting two days before testing and continuing through the test period. Raw fruits and vegetables that contain peroxidase-like substances (turnips, broccoli, horseradish, cauliflower, cantaloupe, parsnips, red radish, etc.) should be avoided during the test period.

What is the effect of medication use on gFOBT positivity?

Literature Search Results

Six studies were found that examined whether medications with anticoagulant properties such as aspirin, NSAIDs, or warfarin produced false-positive results with gFOBTs, where a false positive meant a positive FOBT in an individual who did not have CRC. Three studies involved participants in a screening program (40-42). In two of these studies, no significant difference was observed in the rate of false positives between those taking and those not taking aspirin or NSAID medications (41,42). The third study found a significant (9%) increase in false positives (40). The remaining three studies involved volunteers taking specific amounts of medications, and none of the three found an increase in false-positive results, regardless of the amount taken. Results are detailed in Table 9 below.

A single case report stated that the ingestion of vitamin C supplements might affect gFOBT results (43). This report concluded that the pseudoperoxidase activity of heme was inhibited by the ingestion of large amounts (1,000-2,000 mg/day) of ascorbic acid and that false negative gFOBT results might be associated with the ingestion of vitamin C (43).

In vitro, iron gives a positive guaiac reaction, which may result in false positives (44). However, this was not observed in vivo (45,46). McDonnell et al (46) explained that a pH-dependent event occurring with in vitro iron solutions gives rise to the difference in results.

Table 9. Results of studies examining the effect of medication use on gFOBT positivity.

Study	Study Design	Population	Methods and Results
Clarke et al (40)	Prospective	846 consecutive participants in a screening program with a positive gFOBT and a completed colonoscopy	• All participants were interviewed before colonoscopy to identify regular intake of medication with anticoagulant properties • Of those taking regular medication (number of prescriptions:183–aspirin; 14-COX-2 inhibitor; 113-other NSAID; 26-warfarin), 47.5% had a true positive result • Of those not taking medication, 56.5% had a true positive result • Statistically significant 9% difference (*P* = 0.012). in false positives
Kahi and Imperiale (41)	Prospective	193 consecutive participants in a screening program with a positive gFOBT and a completed colonoscopy	• All participants were interviewed before colonoscopy to identify regular intake (1 daily dose for at least 3 days per week) of aspirin or NSAIDs at time of gFOBT • Of those regular aspirin or NSAID users, 21% had a true positive result, and for nonusers 19% had a true positive result • The difference was not significant (*P* = 0.7)
Greenburg et al (47)	Randomized, double-blind, prospective	40 healthy subjects	• Each volunteer was followed over 30 days taking daily aspirin 30 mg, 81 mg, 325 mg, or placebo. • Subjects completed Hemoccult II and Hemoccult II SENSA FOBTs before and at the end of 30 days • No subject had a positive FOBT.
Greenburg et al (48)	Prospective cross-over	100 asymptomatic participants	• Volunteers were placed in one of three groups: no aspirin or warfarin; daily aspirin (81 or 325 mg); or warfarin for a variety of cardiovascular indications for two months • No increase in the number of positive FOBTs with aspirin or warfarin use
Pye et al (42)	Prospective	455 asymptomatic participants in a screening study with a positive gFOBT and a completed colonoscopy	• All participants were interviewed before colonoscopy to identify NSAID intake at time of gFOBT • Of those taking NSAIDs at the time (N=50) of the gFOBT, 20% had a true positive result • Of those not taking NSAIDs at the time (N=405) of the gFOBT, 32% had a true positive result • The difference was not statistically significant
Norfleet (49)	Prospective	27 healthy volunteers	• Volunteers completed a gFOBT before and after ingesting 1300 mg of aspirin daily for seven days, • All gFOBTs were negative

CRC Screening Program Environmental Scan Results

The results are presented below (Table 10).

Table 10. CRC screening program environmental scan results for medication restrictions.

CRC Screening Program	FOBT Test	Medication Restrictions
NHS Bowel Screening Program	Hema Screen	None
Finnish Cancer Registry	Hemoccult II	Vitamin C supplements should not be used.
National Israeli Breast and Colorectal Cancer Detection Program	Hemoccult II SENSA	None

Internet Search Results

The MDA evaluation reported on samples collected from three individuals consuming various amounts of vitamin C (16). No evidence was found to indicate that a normal level of vitamin C intake (75-90 mg per day, the Recommended Daily Allowance) interferes with gFOBT results. The study concluded that the limit of 250-500 mg per day intake of vitamin C as recommended in many of the package insert instructions for gFOBT is appropriate.

Information Provided in Test Kit Instructions Results

The instructions for medication restrictions from gFOBT kits licensed for sale in Canada are summarized in Table 11 below.

Table 11. Medication restriction recommendations from manufacturers of gFOBT kits available in Canada.

FOBT	Test Kit Recommendations
Hemoccult II	For seven days before and during the stool collection period, avoid NSAIDs such as ibuprofen, naproxen or aspirin (more than one adult aspirin a day). For three days before and during the stool collection period, avoid vitamin C in excess of 250 mg a day from supplements and citrus fruits and juices.
Hemoccult II SENSA	Seven days prior and during testing, no more than one adult aspirin a day (325 mg), no other NSAIDs such as ibuprofen. No more than 250 mg vitamin C a day from supplements, citrus fruits and juices.
ColoScreen	For seven days prior to and during the testing, do not ingest aspirin or other anti-inflammatory medicines. For two days prior to and during testing do not use rectal medicines or tonics or vitamin preparations that contain vitamin C (ascorbic acid) in excess of 250 mg per day.
TRI-SLIDE	Oral medications such as aspirin or other salicylates, NSAIDs such as indomethacin and phenylbutazone, anticoagulants (heparin, coumadin), and corticosteroids, can cause gastrointestinal irritation and bleeding and therefore, inaccurate results. Additionally, colchicines, oxidizing drugs (iodine, bromide, and boric acid), and reserpine have been reported to cause false positive results. On the advice of a physician, these medications might be temporarily discontinued for seven days prior to and during the test period. It is recommended that vitamin C doses in excess of 250 mg daily be discontinued two days prior to and during the test period.
Hema Screen	There are some oral medications such as aspirin, corticosteroids, reserpine, phenylbutazone, and indomethacin that can cause gastrointestinal irritation and occult bleeding in some patients. Ascorbic acid (vitamin C) taken in units greater than 250 mg per day may cause false negative results. Iron or preparations containing iron may cause false positive results. Two days prior to and during the test period, such medications should be avoided.

3. Laboratory Factors

Literature Search Results

Effect of temperature on specimen

No studies were found on the effect of temperature on gFOBTs.

Effect of time interval between specimen collection and laboratory processing

The time interval between specimen collection and laboratory processing can be defined as the number of days between the smearing of the sample on the cards and the development of the sample in the laboratory. Ransohoff and Lang (50) published a clinical guideline regarding the use of FOBTs and their interpretation in CRC screening. They recommended that samples be developed as soon as possible, always within seven days of preparation, since slide positivity may decrease as storage time increases. However, more recent data (39) indicate that a delay in the time to development of three to 14 days is desirable to allow the breakdown of ingested peroxidases.

Young et al (51) added various amounts of hemoglobin to fresh stool samples from a single bowel movement. The stool samples were applied to gFOBT cards either immediately

after defecation or after a 24-hour delay. When cards were smeared immediately, Hemoccult II and Hemoccult II SENSA gave stable results when developed up to 19 days following smearing. However, a 24-hour delay in smearing after defecation decreased sensitivity and test positivity.

Sinatra et al (39) used fecal samples obtained from four healthy subjects following a three-day standard low heme/low plant peroxidase diet. They added varying concentrations of plant peroxidase (HPE) or whole blood to the fecal samples and developed them one, eight, 24, 48, 72, and 144 hours after smearing. They found that, in samples with HPE added, Hemoccult II and Hemoccult II SENSA positivity rates decreased rapidly with time after smearing but reached a plateau at around 48 hours. In samples with whole blood added, the positivity rates increased initially but reached a plateau at around 24 hours.

Staff training

Three studies were found that examined gFOBT interpretation and training. Selinger et al (52) retrospectively reviewed the performance of 162 health care workers with regard to their knowledge and interpretation of gFOBT (Hemoccult II SENSA) results. The health care workers were asked to interpret gFOBT results after participating in a brief gFOBT quality assurance program. The study found that 12% of the health care providers failed to correctly interpret one or more samples, and 28% of providers misinterpreted a sample or answered a question incorrectly, indicating the need for more adequate training prior to attempting to interpret gFOBT results.

Fleisher et al (53) studied the effect of a one-hour FOBT instructional seminar on the ability of program coordinators from the clinical centres participating in the National Polyp Study to correctly interpret FOBT results. Three tests were given, one before the seminar, the second immediately after the seminar, and the third, six to nine months after the seminar. The instructional intervention was associated with a significant improvement in test interpretation over time (60% of cards were read correctly before the seminar, 91% of cards were read correctly afterwards, $p<0.01$), resulting in a reduction in false negatives. This performance improvement persisted over at least a nine-month period.

Niv (54) compared the impact of an inexperienced processor on the interpretation of Hemoccult II FOBT results in a screening program laboratory. The inexperienced processor produced a fourfold higher FOBT positivity (25% versus 6%, $p < 0.01$) and a significantly lower PPV for adenomas greater than one cm (6% versus 25%, $p < 0.05$) than did an experienced processor.

Definition of a positive screening test

Based on their review of the literature Ransohoff and Lang (50) recommended that the definition of a positive gFOBT result was one or more positive windows.

Definition and resolution of an indeterminate result

No studies were found on the definition and resolution of indeterminate results.

CRC Screening Program Environmental Scan Results

The results are presented below (Table 12).

Table 12. CRC screening program environmental scan results for laboratory factors.

CRC Screening Program	FOBT Test	Laboratory Factors
NHS Bowel Screening Program	Hema Screen	Effect of temperature on specimen • The kit includes an addressed plastic envelope which is metallic-lined, to be used to mail the kit when completed, possibly providing some protection against weather conditions. Effect of time interval between specimen collection and laboratory processing • The program follows the manufacturer's recommendation of processing all tests within 14 days of the first use. Generally kits are processed within a day or two of arriving in the laboratory although there can sometimes be a delay in the participant returning the kit. If the sample is too old to process when it reaches the laboratory, this is explained to the participant and s/he is sent a second kit. Staff training • There are only five laboratories so this is relatively simple. There are a limited number of slide developers who are trained in-house. Definition of a positive screening test • A positive screening test is five or six positive windows in a returned kit. Unclear results are those that have less than five "positives" out of the six windows of the kit. For kits with one to four windows positive, the participant is asked to repeat testing with a second kit. Two complete negative results (all six windows) are required before discharging the participant. If the participant returns a second kit with even one window positive, s/he is immediately referred for colonoscopy. Definition and resolution of indeterminate results • An invalid result can be anything that makes kit interpretation difficult, for example, too much material on the card. If this is the case, the participant is sent a repeat kit. Sometimes extensive support is needed for the individual and a telephone helpline is available for participants.
Finnish Cancer Registry	Hemoccult II	Effect of temperature on specimen • The cards are put in the envelope provided by the kit manufacturer and then put into the mail, i.e. no added protection from weather conditions/temperature fluctuations. Effect of time interval between specimen collection and laboratory processing • Minimum 48 hours (two days) after sampling. Staff training • There are a limited number of people trained with the pharmacist at the screening centre.

		Definition of a positive screening test • Not given. Definition and resolution of indeterminate results • Not all windows filled in, torn or broken, wrong side used, or the test too old (more than 14 days from specimen taken). • The screening centre sends a new test kit to individuals with indeterminate results • If the test is too old (more than 14 days from specimen taken), it is processed; if positive, the participant is referred for colonoscopy, if negative, a new test kit is sent.
National Israeli Breast and Colorectal Cancer Detection Program	Hemoccult II Sensa	Effect of temperature on specimen • The kit includes a pre-stamped aluminium return envelope, possibly providing some protection against weather conditions. Effect of time interval between specimen collection and laboratory processing • Samples travel by mail for about 3 days and they wait an extra day or two in the lab before development, for a total mean time of about a week from application. • Samples are processed even if the interval between collection and development is longer than usual, unless it is extremely long (e.g. several week delay, which is rare). Staff training • New technicians are trained by the experienced ones with double reading of positives. Definition of a positive screening test • Not given Definition and resolution of indeterminate results • Not given

Internet Search Results

The Ontario FOBT Pilot Project found differences in gFOBT positivity rates across the regions, which may have been due to differences in the types of gFOBT kits used and/or differences in the protocols of the three laboratories that processed the kits (8).

Information Provided in Test Kit Instructions Results

The instructions for sample storage and processing of gFOBT kits licensed for sale in Canada are tabulated below (Table 13).

Table 13. Storage and processing recommendations for manufacturers of gFOBT kits available in Canada.

FOBT test	Storage and Processing Recommendations
Hemoccult II	Slides containing samples may be stored for up to 14 days at room temperature (15 to 30°) before developing. Slides are best developed no sooner than 3 days after sample application. This allows any fruit and vegetable peroxidases present in the sample to degrade. Slides are to be returned to physician or laboratory no later than 14 days after the first application.
Hemoccult II SENSA	Patients should be instructed to return the slides to the physician or laboratory immediately after preparing the last test. Slides containing samples may be stored for up to 14 days at room temperature (15 to 30°) before developing. Slides are best developed no sooner than 3 days after sample application to allow for degradation of fruit and vegetable peroxidases that may be present in the sample.
ColoScreen	The slide smears may be prepared and developed immediately or stored up to 12 days prior to development.
TRI-SLIDE	Samples may be stored at room temperature away from heat and light for up to 12 days before development. Samples should be tested within seven days of completing the test.
Hema Screen	The tests may be completed and developed immediately, or completed and stored at room temperature, protected from heat and light for up to 21 days before developing.

DISCUSSION

The purpose of this evidentiary review is to evaluate the existing evidence concerning gFOBT kits in order to support the development of standards for Ontario's CRC Screening Program. The standards will provide a basis for selecting the gFOBT kit to be used in the Program and will also determine the laboratory requirements for the Program.

The focus of this document is on gFOBTs performed on six fecal samples (two samples from each of three consecutive, spontaneously passed stools). gFOBT kits are prepared by the participant and then returned to the laboratory for processing. Using the gFOBT to test stool samples obtained during digital rectal examination has a low sensitivity for detecting CRC in asymptomatic individuals (50,55) and was not evaluated here.

The Panel noted that the Ontario CRC Screening Program needs to maximize participation rates. However, an evaluation of the factors that effect participation rates was beyond the scope of this review.

The Panel is aware of two systematic reviews currently underway that evaluate the use of iFOBT for CRC screening. One is being conducted by the Canadian Partnership Against Cancer (CPAC) and the other by the American Cancer Society/US Multi-Society Task Force on CRC. The Ontario CRC Screening Program will review those recommendations when they are published.

gFOBT Performance Factors

In repeated testing, the studies used two FOBT tests (Hemoccult II and Hemoccult II SENSA), two types of samples (rehydrated and unrehydrated), and two definitions of true positives and false negatives. This resulted in a wide range of test positivity (0.8-9.8%), sensitivity (51.1-97%), specificity (90.4-100%), and PPV (2.2-17%) for the detection of CRC. Rehydrating the samples resulted in increased sensitivity and decreased specificity because of the larger number of false positives, which in turn led to an increased need for follow-up colonoscopy.

In most studies that examined gFOBT in single (one-time) testing**,** only those individuals who had a positive screening test underwent colonoscopy (or other follow-up tests), reducing

the accuracy of test performance evaluation. However, in two studies of unrehydrated Hemoccult II all participants underwent colonoscopy. In these studies the sensitivities of unrehydrated Hemoccult II for detecting CRC were 12.9% and 25%, the specificities were 95% and 80%, and the PPVs were 5.5% and 1.0%, respectively.

gFOBT sensitivity is higher in repeated testing than in a single test, because some cancers that were not detected in the initial test are detected in the next round of testing.

The large variation of reported performance characteristics in the literature is in part due to differences in study populations (different diets, ages, or medications); completeness of follow-up for those testing positive and negative; methods of calculating test performance; reference standards; rehydration or nonrehydration of samples; and laboratory protocols (e.g., whether the study waited 48-72 hr to process the samples to decrease ingested peroxidase activity). The Centre for Reviews and Dissemination (CRD) in the UK found the evidence regarding gFOBT performance limited, of poor quality, and containing many potential sources of heterogeneity (17). The CRD concluded that there was little evidence that any particular gFOBT was superior to the others that were evaluated.

The Panel advised that the Program should use a gFOBT kit that achieves a sensitivity ≥ 40% and specificity ≥ 95% for the detection of CRC in repeated testing. These performance standards were chosen after careful review of the evidence on unrehydrated FOBTs, so that the Program has the potential to achieve the CRC mortality reduction published in the literature for repeated gFOBT testing.

In the 19 studies reviewed here, 12 used Hemoccult II and two used Hemoccult II SENSA, four used both and one used Hema Screen. The UK CRC Screening Pilot used Hema Screen and the NHS Bowel Screening Program continues to use it. The Finnish Cancer Registry uses Hemoccult II, and the National Israeli Breast and Colorectal Cancer Detection Program uses Hemoccult II SENSA. The Panel noted that more evidence is available for Hemoccult II and Hemoccult II SENSA than for the other gFOBT kits. The Panel concluded that consistent evidence of superior performance for any particular gFOBT kit is lacking. The Panel recommends, based on the findings from the Ontario gFOBT Pilot Project, that one brand of gFOBT be used to reduce variability in performance.

gFOBT Kit Usability Factors

For each of the usability factors, the quantity and quality of the evidence was uneven. There is not conclusive evidence from RCTs to help inform the recommendations. The existing evidence is mostly from prospective studies, reports, and the opinions of users. Other issues that affected the quality of the evidence and the inconsistency of the results were differences in study populations and the interventions (medication use, diets) that were evaluated. In reviewing the evidence, the Panel considered the Ontario context, and where the evidence was lacking, focused on consensus.

What gFOBT Kit Factors Affect Acceptability by Users?

Studies that evaluated kit factors focused on the method of smearing, the spatula used to collect the smear, the sample window size, and the kit envelopes. These kit factors should be taken into account when deciding which gFOBT kit to use in the Ontario CRC Screening Program.

What is the Effect of Diet Restrictions on gFOBT Positivity?

A meta-analysis found no effect of dietary restriction on gFOBT positivity rates. In addition, diet restriction was not associated with a meaningful reduction in gFOBT kit completion rates except where the dietary restriction was more extensive.

The CRC Screening Programs in the UK and Israel do not advise diet restriction, whereas the Finnish Cancer Registry recommends that participants follow the manufacturer's

instructions. Both Hemoccult II and Hemoccult II SENSA gFOBT kit instructions advise dietary restrictions for three days before and during testing. Hema Screen, TRI-SLIDE, and ColoScreen recommend diet restrictions for two days before and during testing. The Panel recommends that the Ontario CRC Screening Program not impose dietary restrictions but instead have the laboratory delay the processing of fecal samples for a minimum of 48 hours from the time the individual window is smeared.

What is the Effect of Medication Use on gFOBT Positivity?

The literature on this subject is inconsistent. The NHS Bowel Screening Program and the National Israeli Breast and Colorectal Cancer Detection Program do not advise medication restrictions; however, the Finnish Cancer Registry advises against the use of vitamin C supplements. Most kit instructions advise avoiding aspirin or NSAIDs before and during testing, and TRI-SLIDE instructions state that the physician should advise whether medications should be restricted prior to or during the test period. However, since there is insufficient evidence to support having participants discontinue aspirin or NSAIDs, the Panel recommends that the Ontario CRC Screening Program not advise participants to discontinue these medications. All gFOBT kit manufacturer instructions evaluated here advise restricting vitamin C ingestion in amounts greater than 250 mg per day for two days prior to and during testing. Since limiting vitamin C may reduce false negatives, the Panel recommends that participants eliminate vitamin C supplements, citrus fruit and juices for three days prior to and during stool sample collection.

Laboratory Factors

Effect of Temperature on Specimen

No published literature was identified that evaluated the effect of temperature on gFOBT samples. The manufacturers' gFOBT kit instructions state that the samples should be kept at room temperature (15-30^0) but at the same time also discuss mailing the completed gFOBT kits to the laboratory. The Panel discussed mailing the specimens to the laboratory, considering the extreme temperatures that occur in Ontario. However, the Finnish Cancer Registry and the National Israeli Breast and Colorectal Cancer Detection Program, which also expose FOBT specimens to extreme cold and/or heat, use a kit mail-in approach. These programs use special envelopes for the samples that may provide some protection from extremes of weather. The Panel advises that the Program use leak-proof envelopes that protect the samples during mailing, particularly in extreme temperatures.

Time Interval between Specimen Collection and Laboratory Processing

The evidence in the published literature indicated that sample processing for gFOBT is best delayed for 48 hours to allow the breakdown of ingested peroxidases to decrease the number of false positives. The NHS Bowel Screening Program and the National Israeli Breast and Colorectal Cancer Detection Program wait one to two days before processing the samples. The Finnish Cancer Registry waits a minimum of 48 hours. All three programs ensure that the processing is done before 14 days from the first specimen application.

For the five gFOBT kits evaluated here; in two, the kit instructions advise a three-day wait after samples are collected before developing; in two kits, the samples can be developed immediately; and one kit does not provide any recommendations.

The Panel recommends delaying processing for a minimum of 48 hours after sample collection to ensure the breakdown of most peroxidases and thereby decrease the risk of false positives. However, the sample should be developed within the manufacturer's recommended period (12-21 days, depending on the kit). To ensure this happens, the Panel recommends that all key dates relating to the sample be recorded on the specimen. Key dates include the time and date each of the samples was collected, the date the laboratory received the kit, and the

dates that each window was processed. This applies to each of the three stool samples, so that the 48-hour delay in processing can be applied to individual stool samples.

Staff Training

Staff training has a large effect on the reliability and validity of slide interpretation. All surveyed CRC screening programs have developed training programs for their laboratory staff and use only one or a few laboratories to maintain the reliability of test results. The National Israeli Breast and Colorectal Cancer Detection Program has new technicians trained by experienced ones and uses double reading of positives as a part of their training program.

The Panel recommends initial staff training, with retraining at regular intervals, an appropriate quality control (QC) protocol, and constant monitoring of QC data and FOBT results. This is essential to reduce observer variability so that reliable and consistent results are obtained from the laboratory. Consideration should be given to the use of a single laboratory or a limited number of laboratories for the Program.

Findings from the Ontario FOBT Pilot Project also support the need for the Program to use a single gFOBT kit.

Definition of a Positive Screening Test

A positive result has been defined in many studies as one or more positive windows on a test card, and the National Israeli Breast and Colorectal Cancer Detection Program and the Finnish Cancer Registry use this definition. The Panel recommends that a positive result be defined as having one or more positive windows on the test card, regardless of the number of windows completed. Further, if all completed windows are negative, the result is negative.

The completeness of the sample collection (complete is defined as all six windows having samples; incomplete is defined as one or more of the six windows not containing a sample and no positive window), is important to the Program. The Panel recommended that the participant should repeat the gFOBT when it is incomplete, since an incomplete sample card may provide insufficient information regarding fecal occult blood status. The primary care provider should be notified that the test is incomplete and that a new kit has been sent to the participant.

Definition and Resolution of an Indeterminate Result

No information on the definition and resolution of an indeterminate result was found in the literature. Other CRC screening programs report that an indeterminate result can be caused by too much material on the card, a sample that is too old (past the manufacturer's recommended elapsed time for processing, but the sample tests negative), some windows not being filled in, a torn or broken card, or a sample being placed on the wrong side of the card. The Finnish Cancer Registry and the National Israeli Breast and Colorectal Cancer Detection Program both process expired samples and send a new kit to the participant. The NHS Bowel Screening Program sends the participant a new kit. No information was available from the Programs regarding the handling of kits that do not have all the windows completed.

The Panel recommends that a result be considered indeterminate if the result in one or more windows is uncertain, and there are no positive windows. The Panel recommends that the participant be sent another FOBT kit to complete along with a letter explaining why s/he must repeat the test when an indeterminate result occurs.

The Panel discussed the problem of receiving a sample in which one or more of the six windows do not contain a sample or is not processable (the sample is too old, there is too much fecal matter, the kit is physically damaged, the incorrect side of card was used, or the card has expired), meaning that a result cannot be obtained from the sample. The Panel concluded that, in general, if the sample can be processed, this should be done, and if not, the laboratory should send the participant a new FOBT kit with a letter explaining why the kit is being resent.

The Panel also recommends that the number of cards that are positive be recorded and included on the participant report and sent to the primary care provider.

CONFLICT OF INTEREST

One panel member is employed by Gamma-Dynacare Medical Laboratories, which may be a potential conflict of interest. Otherwise, there were no other stated conflicts of interest from other panel members

JOURNAL REFERENCE

The full EBS has been published online in *Clinical Biochemistry* (http://www.sciencedirect.com/science/journal/00099120):

- Rabeneck L, Zwaal C, Goodman JH, Mai V, Zamkanei M. Cancer Care Ontario guaiac fecal occult blood test (FOBT) laboratory standards: evidentiary base and recommendations. Clin Biochem. 2008 Nov;41(16-17):1289-305. Epub 2008 Aug 29. DOI:10.1016/j.clinbiochem.2008.08.069.

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For information about the PEBC and the most current version of all reports,
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Appendix A. Guaiac FOBT Lab Standards Working Panel.

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Appendix B. Results from UK Centre for Evidence-based Purchasing (CEP) evaluation report of three gFOBT kits for issues that affect FOBT processing (15).

FOBT Test	Coloscreen	Hema Screen	Hemoccult
Manufacturer's stated storage time between sampling and analysis	12d	21d	14d
Return envelope	Foil-lined, suitable for posting	Foil-lined, suitable for posting	Bacteria-proof packet, would require an additional envelope for posting
Colour development	Colour good but might be masked by cardboard around test area. Developer did not always spread beyond sample area in all directions.	Satisfactory colour but congested read area. Colour might be masked by surrounding card	Very clear blue colour with adequate space on card to see it. Best for result interpretation
Stated read time	30-120 seconds	30-60 seconds	Within 60 seconds
Time for processing triple test	92 seconds	63-93 seconds	76 seconds
Quality control	Two clearly defined control areas away from test windows	Easily identifiable quality control (QC) across width of card but close to sample windows so may be inadvertently developed at the same time	Clearly defined control areas away from test windows
Ease of use	Easy to process	Easy to process	Easiest to process
Training	Very comprehensive. Two levels: individual competency and competency to train others.	Good quality training and training material	Good quality training material but some discrepancies between documents. Training sessions available if requested.
Customer support	Good	Good	Good

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-Based Series #15-4: Section 3

Guaiac Fecal Occult Blood Test (FOBT) Laboratory Standards Guideline Development and External Review—Methods and Results

L. Rabeneck, C. Zwaal, J. Goodman, V. Mai, and M. Zamkanei:
The Guaiac FOBT Lab Standards Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: November 26, 2007

THE PROGRAM IN EVIDENCE-BASED CARE

The development of the standards was led by the Guaiac FOBT Laboratory Standards Panel, a working group facilitated by the Program in Evidence-Based Care (PEBC), an initiative of Cancer Care Ontario (CCO) (1). 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, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, 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 GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians 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: *Standards***
  This section contains the standards derived by the Guaiac FOBT Laboratory Standards 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 Panel discussion on the topic and the conclusions drawn by the Guaiac FOBT Lab Standards Panel.

- **Section 3: *Methodology of the Standards Development and External Review Process***
  This section summarizes the standards development process and the results of the formal external review by Ontario and international practitioners and CRC screening experts of the draft version of the Guaiac FOBT Lab Standards and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Guaiac FOBT Laboratory Standards Panel. The series is a convenient and up-to-date source of the best available evidence on guaiac FOBT lab factors, 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 standards 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 (CRC) screening experts in Ontario and internationally for their feedback. Section 3 present the feedback process results and any changes made to the draft document.

External Review

Methods

Feedback was obtained through a mailed survey sent to 32 health care professionals and CRC screening experts in Ontario and 15 international CRC screening experts (total=47). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft standards and whether the draft standards should be approved as a provincial guidance document. Participants were invited to provide written comments. The survey was mailed out during the week of July 26, 2007. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Panel reviewed the results of the survey.

Results

Twenty responses were received out of the 47 surveys sent (43% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the 20 responses, 16 completed the survey questions, of these 14 also provided written comments. Four individuals indicated that they were not responsible in some way for the care of patients to whom this standard would apply and did not complete the survey. Key results of the survey are summarized in Table 1.

One hundred percent (16/16) of respondents agreed there exists a need for a standard for this clinical topic, and 93.8% agreed that the draft standards sent to them are achievable. Eighty-one percent of respondents agreed that the evidence was relevant and complete, that the draft standards sent to them were clear, agreed with the methodology used to summarize the evidence, agreed with the draft standards as stated, agreed that the standards reflect a more desirable system for improving the quality of patient care than current practice and that the draft standards should be formally approved. Over 75% of respondents agreed that the draft

standards were in agreement with their understanding of the evidence, and that the standards would be associated with more appropriate utilization of health care resources.

Table 1. Participant responses to survey questions.

1. Are you responsible in some way for the care of patients diagnosed with cancer? This may include direct clinical care or the organization/management of services to provide care to these patients.	**Number (%)**		
	Yes	**Unsure**	**No**
	16	1	3
	Strongly Agree/ Agree	**Neither Agree nor Disagree**	**Strongly Disagree or Disagree**
2. There is a need for a standards document on this topic.	16 (100)	0	0
3. The evidence (literature search and environmental scan) is relevant and complete (e.g., no key information sources or studies missed nor any included that should not have been).	13 (81.3)	1 (6.3)	2 (12.5)
4. I agree with the methodology used to summarize the evidence.	13 (81.3)	2 (12.5)	1 (6.3)
5. The draft standards are in agreement with my understanding of the evidence.	12 (75.1)	3 (18.8)	1 (6.3)
6. The draft standards in this report are clear.	13 (81.3)	2 (12.5)	1 (6.3)
7. I agree with the draft standards as stated.	13 (81.3)	1 (6.3)	2 (12.5)
8. The draft standards are suitable for the Ontario context.	11 (68.8)	3 (18.8)	1 (6.3)
9. The draft standards are too rigid to apply in the Ontario context.	1 (6.3)	3 (18.8)	11 (68.8)
10. When applied, the draft standards will produce more benefits for patients than harms.	13 (81.3)	2 (12.5)	1 (6.3)
11. The draft standards report presents a series of options that can be implemented.	13 (81.3)	2 (12.5)	1 (6.3)
12. To apply the draft standards will require reorganization of services/care in my practice setting.	5 (31.3)	5 (31.3)	5 (31.3)
13. The standards will be associated with more appropriate utilization of health care resources.	12 (75.1)	3 (18.8)	1 (6.3)
14. The draft standards in this report are achievable.	15 (93.8)	1 (6.3)	
15. The draft report presents standards that are likely to be supported by a majority of my colleagues.	11 (68.8)	3 (18.8)	2 (12.5)
16. The draft standards reflect a more desirable system for improving the quality of patient care than current practice.	13 (81.3)	2 (12.5)	0
17. I would feel comfortable if patients received the care recommended in these draft standards.	13 (81.3)	3 (18.7)	0
18. These draft standards should be formally approved.	13 (81.3)	1 (6.3)	1 (6.3)
	Likely/Very Likely	**Unsure**	**Not at All/Not Likely**
19. If these draft standards were to be approved and endorsed, how likely would you be to apply the recommendations to the clinical care or organizational and/or administrative decisions for which you are professionally responsible?	10 (62.5)	1 (6.3)	2 (12.5)

* Where percentages total <100%–practitioner response(s) missing.

Summary of Written Comments

Most respondents also provided written comments. The major themes emerging from these comments were:

1. There were some formatting issues and requests for added information from some of the studies already included and a suggestion to add one other paper regarding laboratory processes.
2. It was felt that the determination of the recommended sensitivity and specificity values for the Program required more explanation.
3. It was felt that vitamin C should be limited for three days and that the recommendation should also limit juices and citrus fruits.
4. The Panel should consider exclusion of red meat for 3 days.
5. Need an explanation for the information such date of birth on card.
6. No evidence that the results of each window should be recorded rather than each specimen.
7. Concern about physicians not receiving the gFOBT results
8. Concern over the source of the definition of a positive result.

Modifications/Actions

The feedback and comments were brought back to the Panel for discussion and the following modifications were made:

1. The dates of the studies were added to the Tables 3 and 4. As well, the number of kits evaluated was added to the MDS report (page 11) and the numerical value for significant improvement in test interpretation resulting from instructional intervention was added to the Fleisher Study (page 19). The additional paper was not added because the Panel determined that the results did not add further information.
2. The decision process for sensitivity and specificity values was clarified in the discussion.
3. The Panel agreed and made the recommendation for 3 days and added that juices and citrus fruits should also be limited
4. The Panel felt that the exclusion of red meat was not necessary based on the findings in the literature.
5. The addition of the date of birth is required because the Ontario Laboratory Accreditation Program (OLA) requires that each specimen received by a laboratory for testing is identified with two unique identifiers. In Ontario, the full name is one unique identifier and the second is either the OHIP Health Card number or the birth date. In the case of the FOBT program, the birth date serves two purposes. In the absence of the Health Card number it becomes the second unique identifier and it also provides the age of the patient, should the Program wish to age-stratify the FOBT results.
6. The Panel changed the recommendation so that the results for each card should be recorded.
7. The Panel recommended that the primary care physicians receive all results as well as be notified when the sample is incomplete or not processable.
8. The definition of a positive result is from Ransohoff and Lang (which is cited in the references) based on their review of the literature.

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the PEBC Report Approval Panel in August 2007. The Panel consists of three PEBC managers with expertise in methodology issues. Key issues raised by the Panel included: a) a need for more description of the screening terms and methodologies; b) the need to summarize the literature used in each aspect of the Evidence-Based Series; c) better clarity needed in the summary of

evidence used in the performance factors section; and d) the need to be more specific regarding state of the evidence in the discussion.

In response to these issues, the following actions were taken: a) a table was added to the introduction describing screening methodologies; b) a table was added in the methods section totalling the number and types of studies used to inform each section of the standards; c) the results for the performance standards section was completely rewritten to provide clarity and a better understanding of the evidence and d) the discussion section was rewritten in order to add information regarding the state of evidence in the document and the evidence used to develop the recommendations, as well information was added describing the consensus process and when consensus was used in development of the recommendations.

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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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