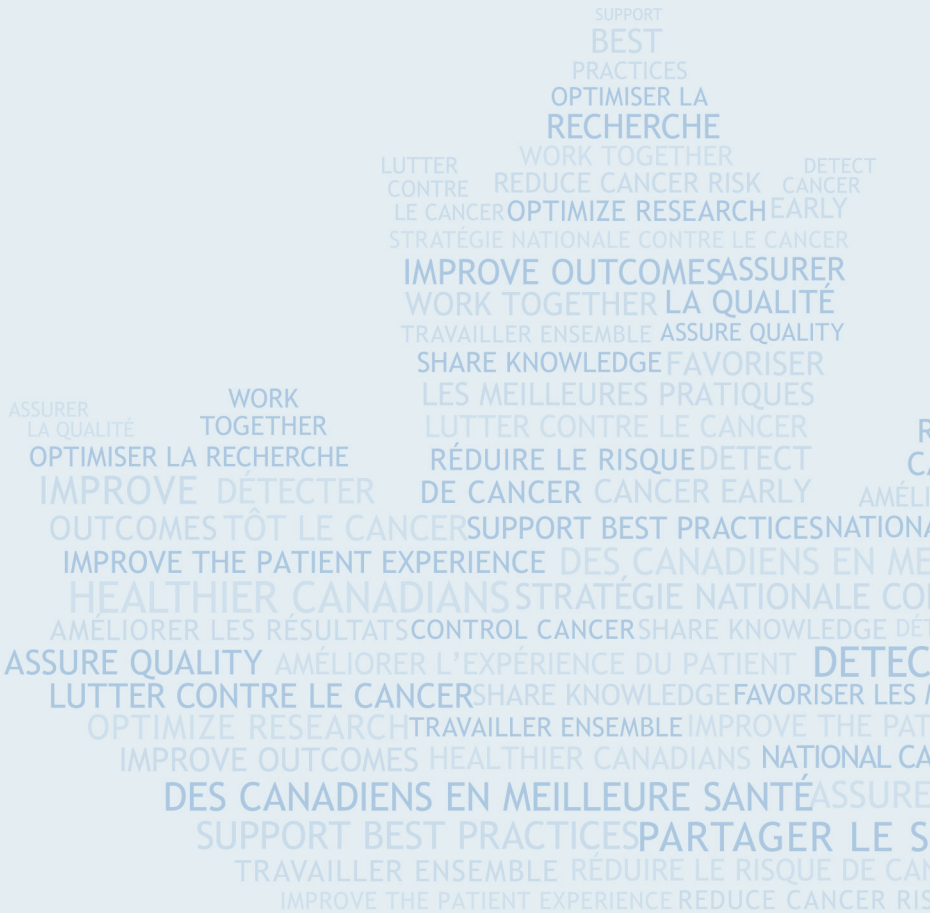
CANADIAN PARTNERSHIP AGAINST CANCER | PARTENARIAT CANADIEN CONTRE LE CANCER

SCREENING PORTFOLIO

Colorectal Cancer Screening – Flexible Sigmoidoscopy

Expert Panel: Summary of Existing and New Evidence

September 19, 2012



ANTICIPATORY SCIENCE

a summary of existing and new evidence

Table of Contents

Expert Panel Members

Dr. Linda Rabeneck – co-Chair
linda.rabeneck@cancercare.on.ca

Professor of Medicine, University of Toronto

VP, Prevention and Cancer Control, Cancer Care Ontario

Dr. Verna Mai – co-Chair
verna.mai@partnershipagainstcancer.ca

Expert Lead Screening, Canadian Partnership Against Cancer

Dr. Andrew Coldman
acoldman@bccancer.bc.ca

Vice President, Population Oncology, BC Cancer Agency

Ms. Marion Harrison
marion.harrison@cancercare.mb.ca

Director, Screening Programs, Cancer Care Manitoba

Ms. Virginia Flintoft
virginia.flintoft@utoronto.ca

Patient Representative and Project Manager, Central Measurement Team, SHN Health Policy, Management and Evaluation, University of Toronto

Dr. Harminder Singh
singh@cc.umanitoba.ca

Assistant Professor of Medicine, Departments of Medicine and Community Health Sciences, University of Manitoba

Dr. Heather McLean
mcleanh@tbh.net

Family Physician and Regional Primary Care Lead, Northwestern Ontario Regional Cancer Centre

Dr. Robert Hilsden
rhilsden@ucalgary.ca

Associate Professor, Departments of Medicine and Community Health Sciences, University of Calgary

Dr. Lisa Del Giudice
lisa.delgiudice@sunnybrook.ca

Family Physician, Sunnybrook Health Sciences Centre

Primary Care Cancer Lead, Toronto Central LHIN

Dr. Alaa Rostom
arostom@ucalgary.ca

Associate Professor, Departments of Medicine, and Community Health Sciences

Medical Director, Forzani & Macphail Colon Cancer Screening Centre

Dr. Bernard Candas
bernard.candas@inspq.qc.ca

Chercheur, Unité d'Analyse des politiques de dépistage et de lutte contre les maladies chroniques

Direction de l'analyse et de l'évaluation des systèmes de soins et services, Institut National de Santé Publique du Québec

Summary Statement of the Panel

The recently published results from the U.S. PLCO trial, along with the U.K. FS, Italy (SCORE) and Norwegian (NORCCAP) trial results provide clear evidence that screening with flexible sigmoidoscopy reduces both colorectal cancer incidence and mortality in average risk individuals.

The PLCO trial reported a significant reduction of 26% and 21% in CRC mortality and incidence respectively in the screening arm (compared to the control usual care arm) in average risk individuals aged 55-74. The results from three of the trials show a statistically significant reduction in incidence of colorectal cancer and two of the trials found statistically significant reductions in colorectal cancer mortality. Flexible sigmoidoscopy needs to be considered as an option in organized colorectal cancer screening programs in Canada.

Purpose

This document provides a concise synthesis of the results of four flexible sigmoidoscopy (FS) randomized controlled trials (RCTs) for colorectal cancer (CRC) screening. The results of each trial were highlighted in its own Watching Brief or Supplement to a Watching Brief. Two Watching Briefs and two Supplements to Watching Briefs have been published:

- June 2009 – Watching Brief 1 with a focus on the NORCCAP trial results.
- June 2010 – Watching Brief 2 with a focus on the U.K. FS trial results.
- October 2011 – Supplement to Watching Brief 2 with a focus on the SCORE trial results.
- May 2012 – 2nd Supplement Watching Brief 2 with a focus on the PLCO trial results.

All information from past Watching Briefs 1 and 2, and the two supplements to Watching Brief 2 have been consolidated in this document. This document also includes the PLCO trial results. The Expert Panel provides its perspectives on the benefits and adverse effects of FS for CRC screening. The document also addresses the quality and limitations of the evidence. Health policy advisors and provincial/territorial cancer agencies will benefit from this overview of the FS trial results, putting them into the context of CRC screening in Canada.

This document is not intended to provide definitive answers or clinical and policy recommendations.

Flexible Sigmoidoscopy

FS is an endoscopic procedure in which a flexible fiberoptic instrument is used to examine the rectum and lower (distal) colon, unlike colonoscopy, which examines the rectum and total (upper and lower) colon

Adenomas, which are premalignant precursors to CRC, divided by location and presence of advanced histology. Advanced adenomas are those with features placing them at increased risk for progressing to cancer (size ≥ 1 cm, villous histology or high-grade dysplasia).

The use of FS as a CRC screening test was examined in four randomized controlled trials (see Table 1).

Most clinical practice guidelines recommend FS screening every five years. The three European trials evaluated a single FS at age 55–64 years while the PLCO trial evaluated two rounds of screening.

Acceptability and anticipated uptake of FS in population-based CRC screening programs in Canada is unknown. High participation rates were observed in the NORCCAP and PLCO trials (67% and 86.6% had at least one screen). However screening attendance rates were much lower in two other FS trials that first invited eligible individuals to indicate their interest in screening, before randomizing those who were interested (see 'Uptake' section in Table 1) and in a Dutch study that compared participation among those offered FS and those offered FIT (32% for FS vs. 62% for FIT).[1]

In the FS trials, the proportion of screened individuals requiring colonoscopy varied from 5% to 21.9% depending on the permissiveness or restrictiveness of the criteria for colonoscopy (see Table 1). The highest colonoscopy rate was in the PLCO trial and the lowest was in the U.K. FS trial. Flexible sigmoidoscopy can lead to the detection of proximal (defined as proximal to the sigmoid colon) adenomas and cancers if there are distal (defined as rectum and sigmoid colon) adenomas that lead to a complete colonoscopy. Whether the presence of any neoplasia on FS was an indication for colonoscopy appears to be a major factor in determining the subsequent colonoscopy rate, as can be seen when comparing the NORCCAP and U.K. FS trials. The incidence and mortality results are summarized in Tables 2 and 3.

Table 1: Key Features of Flexible Sigmoidoscopy Randomized Controlled Trials

FEATURES	NORCCAP[2]	U.K. FS[3,4]	SCORE[5,6]	PLCO[7,8]
STUDY				
Country	Norway	U.K.	Italy	U.S.
Lead investigator	Hoff, G.	Atkin, W.S.	Segnan, N.	Weissfeld, J.
Recruitment period	1999-2000	1996-1999	1995-1999	1993-2001
POPULATION				
Number randomized	55,736	170,432	34,292	154,000
Setting	2 areas: 1 city, 1 country	14 centres	6 trial centres: Arezzo, Biella, Genoa, Milan, Rimini, Turin	10 cities
Source	Population	General practice	1. General practice	Public, commercial,

FEATURES	NORCCAP[2]	U.K. FS[3,4]	SCORE[5,6]	PLCO[7,8]
	registry	registry	patient registry (Arezzo, Rimini, Turin) 2. Volunteer practices (Milan) 3. Health services registry (Biella, Genoa)	screening centre mailing lists
Age (years)	55-64	55-64	55-64	55-74
STUDY GROUPS				
Randomization	Before invitation	After invitation	After invitation	After invitation
Study arms	1. FS 2. FS & FIT 3. No screening	1. FS 2. No screening	1. FS 2. No screening	1. FS 2. No screening
POWER CALCULATION ASSUMPTIONS				
Screening arm(s) (n)	7,000 FS 7,000 FS & FIT	65,000	20,000	74,000
Control arm (n)	42,000	130,000	20,000	74,000
Compliance (%)	70	55 (up to 5% contamination in control arm)	70	85 (up to 15% contamination in control arm)
CRC incidence reduction (intent to treat) (%)	30	20	21	NR
CRC mortality reduction (intent to treat) (%)	NR	20	NR	15
Follow-up (incidence) (years)	5	10	6	NR
Follow-up (mortality) (years)	5	15	11	10
Significance level (%)	5 (two-sided)	5 (two-sided)	5 (one-sided)	5 (one-sided)
Power (%)	90	90	80	90
UPTAKE				

FEATURES	NORCCAP[2]	U.K. FS[3,4]	SCORE[5,6]	PLCO[7,8]
Responded to invitation~ (%)	NR	74	83	NR
Interested in screening (invited)* (%)	NR	55	16	NR
Attended screening (randomized)† (%)	67	71	58	86.6**
Attended screening (invited)‡ (%)	67	39	9	86.6**
SIGMOIDOSCOPY				
Instrument	140cm colonoscope	60cm videoscope	4 centres: 140 cm colonoscope 1 centre: sigmoidoscope	60cm flexible sigmoidoscope
Endoscopist	NR	Registrar-level gastroenterologists & surgeons	Gastroenterologists	Physicians, nurse practitioners
Screen frequency	Once only	Once only	Once only	Baseline, year 5
Criteria for colonoscopy	1. Any polyp ≥ 10mm 2. Any neoplasia	1. Any polyp ≥ 10mm 2. ≥ 3 adenomas 3. Any polyp with villous component or severe dysplasia 4. Any cancer 5. ≥ 20 hyperplastic polyps above distal rectum	1. Any polyp ≥ 5mm 2. Any polyp + inadequate bowel prep 3. ≥ 3 adenomas 4. Any polyp with villous component ≥ 20% or severe dysplasia 5. Any cancer 6. ≥ 5 hyperplastic polyps above distal rectum	Any polypoid lesion or mass
Proportion requiring colonoscopy (%)	20.4	5.2	5.3	21.9

FS = flexible sigmoidoscopy; FIT = immunochemical fecal occult blood test; NR = Not Reported.
~ Proportion of individuals who responded to an invitation from those with a delivered invitation.
* Proportion of individuals interested in screening from those with a delivered invitation.
** Proportion who attended at least one screen out of the 2 screening rounds in the trial
†Proportion of those with delivered invitation that were interested in screening and attended for FS.
‡Proportion of those with delivered invitation that were interested in screening and attended for FS (Product of Interested in Screening and Attended Screening – Randomized).

Table 2: Colorectal Cancer Incidence Results from Flexible Sigmoidoscopy Randomized Controlled Trials (intervention vs. control groups, relative risk (95% confidence interval))

Trial	Incidence Results		
	All Colorectal Cancers	Distal Cancers*	Proximal Cancers
NORCCAP[2]	134.5 vs. 131.9/100,000 person years (no difference)	NR	NR
U.K. FS[4]	0.77 (0.70-0.84)	0.64 (0.57-0.72)	0.98 (0.85-1.12)
SCORE[6]	0.82 (0.69-0.96)	0.76 (0.62-0.94)	0.91 (0.69-1.20)
PLCO[8]	0.79 (0.72-0.85)	0.71 (0.64-0.80)	0.86 (0.76-0.97)

NR = Not Reported

* Distal cancers were defined as those occurring in the rectum and sigmoid colon in the NORCCAP and UK FS trials; those occurring in the descending colon, sigmoid colon, or rectum in the SCORE trial and those occurring in the splenic flexure, descending colon, sigmoid colon or rectum in the PLCO trial. Changing the definition of distal cancers to include only cancers occurring in the sigmoid colon or rectum was reported to have little effect on the incidence or mortality results in the PLCO trial. The SCORE trial reported a similar reduction in descending colon cancer incidence as for the sigmoid and rectal cancers.

In three trials, significantly reduced cumulative CRC incidence in the intervention group was reported, mostly in the distal colon. In the NORCCAP trial differences were not observed however follow-up was shorter making the effect of prevalent cancer harvesting more pronounced.

There was a statistically significant reduction in CRC mortality in two of the four trials (U.K. FS and PLCO). Although the mortality results of the NORCCAP and SCORE trials were not statistically significant, the estimates were similar to those of the U.K. FS and PLCO trials (see Table 3). The NORCCAP and SCORE trials included smaller numbers of study subjects than in the other two trials, which is likely responsible for the wider confidence intervals in the results from the NORCCAP and SCORE trials.

The U.K. FS trial demonstrated an overall 23% reduction in CRC incidence and a 31% reduction in CRC mortality. In a secondary analysis, when the investigators examined the effect of screening in participants (those who do not participate are included in the analysis to adjust for self-selection bias), the incidence was reduced by 33% and CRC mortality by 43%. The incidence of distal CRC (rectum and sigmoid) was reduced by 36% (intention-to-treat) and 50% (per protocol). There was no reduction in the incidence of proximal cancers (proximal to the sigmoid colon). The investigators did not provide mortality results for proximal and distal CRC.

Although statistically significant results were reported in three of the four trials for per protocol analyses (comparing screening attendees to the control group), this type of analysis is prone to self-selection bias, which is a serious concern. Those attending screening may differ from those who did not and from the controls. Those who attended screening may be at lower risk of CRC than the control population ("healthy screenee" effect). For example, they may be of higher socioeconomic status, live healthier lifestyles or be more vigilant about their health. Although adjustments address some potential biases, intent to treat analyses are preferred.

Table 3: Mortality Results from Flexible Sigmoidoscopy Randomized Controlled Trials

Mortality Results	Intervention vs. control group (intent-to-treat analysis), hazard ratio (95% CI)	Screening vs. non-screening* (per protocol analysis), hazard ratio (95% CI)
ALL CRC MORTALITY		
NORCCAP[2†]	0.73 (0.47-1.13)	0.41 (0.21-0.82)‡
U.K. FS[4]	0.69 (0.59-0.82)	0.57 (0.45-0.72)
SCORE[6]	0.78 (0.56-1.08)	0.62 (0.40-0.96)
PLCO[8]	0.74 (0.63-0.87)	NR
DISTAL CANCER MORTALITY**		
NORCCAP[2†]	0.63 (0.34-1.18)	0.24 (0.08-0.76)‡
U.K. FS[4]	NR	NR
SCORE[6]	0.73 (0.47-1.12)	0.48 (0.24-0.94)
PLCO[8]	0.50 (0.38-0.64)	NR
ALL-CAUSE MORTALITY		
NORCCAP[2†]	1.02 (0.98-1.07)	NR
U.K. FS[4]	0.97 (0.94-1.00)	0.95 (0.91-1.00)
SCORE[6]	Hazard ratio not reported; only rates (660.26/100,000 person-years in control vs. 640.96/100,000 in intervention group)	NR
PLCO[8]	NR	NR

*Sub-analysis of the effect of screening in participants.
** Distal cancers were defined as those occurring in the rectum and sigmoid colon in the NORCCAP and U.K. FS trials; those occurring in the descending colon, sigmoid colon or rectum in the SCORE trial and those occurring in splenic flexure, descending colon, sigmoid colon or rectum in the PLCO trial. Changing the definition of distal cancers to include only cancers occurring in the sigmoid colon or rectum was reported to have little effect on the incidence or morality results in the PLCO trial. The SCORE trial reported similar reduction in descending colon cancer incidence as for the sigmoid and rectal cancers.
†Results are for FS and FS + FIT groups combined.
‡Note that the NORCCAP screening vs. non-screening analysis does not adjust for self-selection bias; therefore, caution is advised when interpreting these results.
NR = Not Reported

Limitations and Potential Harms of Flexible Sigmoidoscopy

FS is an endoscopic procedure, and requires bowel preparation beforehand in order to maximize the ability of the endoscopist to visualize the distal colon. However, the bowel preparation is much simpler and less time consuming for the patient to complete than that required for colonoscopy. Some of the main immediate harms include physical discomfort for some patients and, while very uncommon, perforation of the bowel can occur (e.g. 2.8/100,000 in the PLCO trial). An abnormal screening examination with FS requires that an individual undergo a colonoscopy, which is carried out during a subsequent appointment for the procedure. There is a small risk of adverse events from colonoscopy, including perforation. In the PLCO trial, the rate of perforation for those undergoing diagnostic colonoscopy was 107.5/100,000.

The rate of abnormal screens referred for follow-up colonoscopy in the four trials varied greatly from a low of 5% to 21.9%, depending on the screening protocol. Higher abnormal screen rates will subject more individuals to colonoscopy follow-up and potentially higher false positive results. The PLCO reported false positive rates of 20% in men and 13% in women.

FS is an examination that covers only the distal portion of the colon. While results from the PLCO trial have demonstrated that the incidence of proximal cancers can be reduced as a result of FS screening and subsequent follow-up colonoscopy, there has not been a significant reduction of mortality from proximal CRC seen in any of the four trials. While the lack of proximal CRC impact is considered a limitation of FS, it should be noted that it is not known to what degree screening with colonoscopy might demonstrate more significant results. Proximal cancers are often more difficult to detect as flatter, advanced serrated adenomas tend to be more prevalent in the proximal colon.

Fecal Occult Blood Test

Hemoccult Fecal Occult Blood Test

Several published RCTs used earlier versions of the Hemoccult FOBT (Hemoccult or Hemoccult II).[9-12] Hemoccult tests rely on the pseudo-peroxidase activity of haemoglobin in stool. They are referred to as aiac FOBTs (gFOBTs). The results of the gFOBT RCTs were pooled and summarized in a 2008 Cochrane review (Tables 4 and 5).[13] The pooled results indicated:

- That a CRC screening program with biennial gFOBT can lead to a 16% reduction in CRC mortality after 12 to 18 years.
- There was a 25% CRC mortality reduction (RR 0.75, 95% CI: 0.66–0.84) for those attending at least one round of gFOBT screening.
- The uptake/compliance for gFOBT was high, with approximately two-thirds of study participants attending at least one round. A high uptake may be challenging to sustain over repeated rounds of screening, however. A UK pilot study, found similar uptake and test characteristics (but without data on CRC mortality) of one-time FOBT, as demonstrated in the RCT in UK.[10]

It has been estimated that if a biennial gFOBT-screening program was offered to 10,000 people, and if two-thirds had at least one gFOBT, 8.5 deaths (95% CI: 3.6–13.5) from CRC would be prevented over 10 years.[14]

Annual (rather than biennial) FOBT has been evaluated in only one RCT – the study from the U.S.[15] Based on this RCT and modelling studies,[16,17] it has been suggested that annual FOBT screening can lead to more life-years gained than biennial screening. However, the resources required for annual screening are greater than for biennial screening.

Current provincial CRC screening programs, underway or in the planning stages, may implement biennial or annual screening.

Up until the published results of FS RCTs, gFOBT use had shown the strongest evidence of efficacy among all tests available for CRC screening.

Table 4: Key Features of gFOBT Randomized Controlled Trials

	Minnesota[9]	U.K.[10]	Denmark[11]	Sweden[12]
Study population (N)	46,445	152,850	61,933	68,308
Ages (years)	50-80	45-74	45-75	60-64
Screening cycles	Annual, biennial	Biennial	Biennial	Biennial
No. of Screening rounds (N)	11 (annual) 6 (biennial)	6	9	2
Follow-up (years)	18	11.7	17	15.5

	Minnesota[9]	U.K.[10]	Denmark[11]	Sweden[12]
Compliance, first screening (%)	NR	53	67	63
Compliance, at lease one round (%)	75 (annual) 78 (biennial)	60	NR	70
Completion of all rounds (%)	46 (annual) 60 (biennial)	38	46	NR

Note: European trials randomly allocated subjects to invitation or no invitation for screening. Minnesota study included only those who had agreed to participate.
NR: Not reported

Rehydrated FOBT as used in the Minnesota trial is not routinely used in clinical laboratories or in clinical practice and is not recommended by any CRC screening clinical practice guideline. When rehydrated the positivity rate of the test is increased with increased sensitivity and decreased specificity.

The sensitivity for CRC given in Table 5 is for a program of annual or biennial testing and not for a single episode of testing. The sensitivity of a single set of unrehydrated FOBTs compared with colonoscopy has been reported to be as low as 13%.[18]

Table 5: Results of gFOBT Randomized Controlled Trials

		Minnesota[9, 15]	U.K.[10]	Denmark[11]	Sweden[12]	Cochrane Meta-analysis[13]
Test positivity (%)	**Unrehydrated**	1.4-5.3	1.2-2.7	0.8-3.8	1.9	NR
	Rehydrated	3.9-15.4	NR	NR	1.7-14.3	NR
Cumulative colonoscopy rate (%)	**Annual**	38	NR	NR	NR	NR
	Biennial	28	2.6	5.3	6.4	NR
Sensitivity for colorectal cancer (%)	**Unrehydrated**	80.8	57.2	55	NR	NR
	Rehydrated	90.2	NR	NR	82	NR
PPV for colorectal cancer (%)	**Unrehydrated**	5.6	9.9-11.9	5.2-18.7	NR	NR
	Rehydrated	0.9-6.1	NR	NR	NR	NR
PPV for adenomas (%)	**Unrehydrated**	6.0-11.0	42.8-54.5	14.6-38.3	NR	NR
	Rehydrated	NR	NR	NR	NR	NR
Cumulative incidence ratio screening to	**Annual**	0.80 (0.70-0.90)	NR	NR	NR	NR

		Minnesota[9, 15]	U.K.[10]	Denmark[11]	Sweden[12]	Cochrane Meta-analysis[13]
control (95% CI)	**Biennial**	0.83 (0.73-0.94)	NR	NR	NR	NR
Colorectal cancer mortality – RR (95%)	**Annual**	0.67 (0.51-0.83)	NR	NR	NR	NR
	Biennial	0.79 (0.62-0.97)	0,87 (0.77-0.97)	0.84 (0.73-0.96)	0.84 (0.71-0.99)	0.84 (0.78-0.90)
All-cause mortality – RR (95% CI)		1.00 (0.97-1.02)	1.00 (0.99-1.02)	1.00 (0.98-1.02)	1.02 (0.99-1.04)	1.00 (0.99-1.03)

NR = Not Reported
PPV = Positive predictive value

Other Fecal Occult Blood Tests and Fecal Immunochemical Tests

Hemoccult Sensa is a guaiac-based FOBT (gFOBT) developed to improve the sensitivity of Hemoccult. This test also has a lower specificity than Hemoccult. A different technology has been used to develop the fecal immunochemical test (FIT), which is specific to human globin unlike gFOBTs.

The accuracy of the newer FOBTs was the subject of a recent systematic review for the U.S. Preventive Services Task Force (USPSTF).[19] The review concluded that Hemoccult II was less sensitive than FIT for CRC detection and that FIT's sensitivity was similar to or less than that of Hemoccult Sensa. The specificity of Hemoccult Sensa was reported to be less than that of FIT, which had specificity similar to that of Hemoccult II. However it must be noted that FITs produced by different manufacturers do not have identical properties. The review noted, however, that there are few studies directly comparing different FITs with each other or with regular or high-sensitivity Hemoccult tests (Hemoccult Sensa). FITs offer further potential advantages. They provide a quantitative score rather than qualitative results as gFOBTs do. This permits the user specification of the threshold of abnormality detected and the threshold selected influences the resulting sensitivity and specificity. They also have collection kits that are typically easier to use by participants.

An earlier review by the U.S. Multi-Society Task Force on Colorectal Cancer had concluded that there were no clear patterns of difference in sensitivity and specificity between Hemoccult Sensa and FIT.[20] Though there are no data on the impact of screening with Hemoccult Sensa or the FIT on CRC mortality or incidence a decision analysis conducted for the USPSTF estimated that given better test characteristics, Hemoccult Sensa and FIT could potentially demonstrate better CRC mortality reduction than the earlier versions of gFOBT.[17]

Two recent RCTs in the Netherlands reported that the uptake of FIT (OC Sensor) was more than 10% higher than that of Hemoccult II and that specificity may be as high as with gFOBT at a positivity threshold of 200 ng/ml.[1,21] Uptake of Hemoccult Sensa in target populations has also been reported to be lower than for the FIT. This was likely due to the greater number of stool specimens required, method of specimen collection and/or dietary restrictions prior to and during sample collection.[22] Moreover, the removal of inter-observer variation in test interpretation due to automated analysis makes any FIT appear more advantageous. Currently, more extensive data exist for FIT than for Hemoccult Sensa.[23]

Limitations of Fecal Occult Blood Tests

FOBTs have demonstrated no direct harms but they do have the following limitations:

- False positive tests lead to further testing with colonoscopy, which introduces the potential for harms.
- FOBTs have lower sensitivity (< 50%) for advanced adenomas than CRC.[24,25] Due to the lower sensitivity, CRC incidence reduction (20%) has been demonstrated in only one RCT using rehydrated gFOBT and after 18 years of follow-up.[9]

Considerations for Adopting Flexible Sigmoidoscopy in Population-based Screening Programs

Implication of Study Design Differences for Screening Programs

If a jurisdiction wished to implement a screening program using FS it would be important to consider the key differences between how FS was performed in the published studies (Table 1).

Consider the two largest studies: UK FS trial and PLCO. In the PLCO trial, 21.9% of those screened by FS required a colonoscopy, whereas only 5.2% required a colonoscopy in the UK FS trial. Despite nearly five times the number of people undergoing a colonoscopy in the PLCO trial, the CRC mortality reduction was similar for the two trials (Table 3). To achieve these results, those performing FS in the UK FS trial had to remove identified polyps at the time of the FS, something that is not routinely done in most settings. This required the use of CO2 insufflation as a non-combustible gas allowing for snare polypectomy with cautery to be performed and the use of specialist endoscopists trained in polypectomy.

In contrast, the PLCO trial did not require specialist endoscopists and in fact some procedures were performed by nurse practitioners. Non-specialist physicians and nurse practitioners are usually not trained in polypectomy techniques.

Therefore, the PLCO minimized the resource requirements for FS at the expense of higher resource demands on colonoscopy services. Whereas, the UK FS trial minimized the demands upon the colonoscopy service at the expense of requiring higher level endoscopists and special equipment for flexible sigmoidoscopy.

Of note, when interpreting and comparing the results from different trials other key differences in the conduct of these studies should also be kept in mind, for example in PLCO the estimated rate of contamination in the usual care group in the screening phase was 46.5% for either FS or colonoscopy. This might have reduced the beneficial effect seen with FS in PLCO. There was minimal contamination in the UK FS trial.

Infrastructure Resources

The resources to provide FS include the following:

Setting or Facility: FS requires an appropriate setting in which to perform the un-sedated procedure. FS can be performed in an endoscopy room or an operating room in a hospital, or in an ambulatory endoscopy clinic, although this would require an appropriate funding model (see below). In the past, FS may have been performed in an office setting, but this practice would likely not meet current standards for infection control (see below).

Equipment: FS can be done using a 60cm long fiberoptic sigmoidoscope or it can be done using the longer colonoscope.

Endoscopy Capacity: Regardless of where FS is performed, adequate capacity is required; that is, the resources must be available specifically for this purpose. FS may be perceived as displacing colonoscopy if, for example, endoscopy rooms currently dedicated to colonoscopy are used for FS. An expansion of endoscopy capacity is required; otherwise the introduction of FS could adversely affect access to colonoscopy.

Infection Control: Reprocessing (or cleaning) used sigmoidoscopes requires the same reprocessing used for colonoscopes (manual cleaning followed by chemical disinfection using dedicated equipment – a "scope washer"). Reprocessing needs to be performed by individuals specifically trained in cleaning and

disinfecting procedures. Typically, in a large hospital-based endoscopy unit, a dedicated endoscopy technician cleans the scopes.

Endoscopists: FS can be performed by appropriately trained physicians, such as gastroenterologists, general surgeons, and family physicians (FPs) as well as appropriately trained non-physicians including RNs (RN-FS). Polyp detection rates, depth of endoscope insertion, complication rates and patient satisfaction are no different for appropriately trained non-physician and physician endoscopists performing FS.[26] Few FPs currently perform FS or have been trained to do FS in Canada. Ontario is piloting RN-FS and has set up a training program at The Michener Institute for Applied Health Sciences in Toronto to train nurses to do FS. If other provinces undertake non-physician FS, formal training programs will be required.

Endoscopy Assistants: Regardless of whether a physician or non-physician endoscopist performs FS, a trained endoscopy assistant is needed to assist the endoscopist with the procedure.

Reimbursement/Funding Model: Funding required for endoscopy by physicians consists of physician compensation and facility funding (which covers the non-physician costs of providing the service). Physicians who perform FS are reimbursed by provincial health insurance plans. Currently since there is either no fee or an insufficient "technical fee" in the fee schedules (that would cover the costs of providing the service), it is not financially viable for an individual physician or group of physicians to provide FS outside of a hospital setting. If appropriately trained non-physicians were to perform FS screening, presumably they would be salaried, and the costs of providing the equipment, endoscopy room time, etc. would need to be provided.

Clinical and Programmatic Issues

Biopsy of Lesions Detected at FS: When a polyp is detected at FS, it can be biopsied and removed as long as it is small and electrocautery is not required. If non-physicians were to perform FS screening, they will need to be able to perform these biopsies. For example, in the Ontario RN-FS pilot, nurses are trained to remove lesions up to 3 mm in size, using cold biopsy.

Criteria for Referral to Colonoscopy: Some individuals in whom abnormal lesions are detected at FS will need to be referred for colonoscopy. For those in whom masses or other lesions suspicious for cancer are identified at FS, the need for referral is straightforward. For those in whom one or more polyps are identified, criteria for referral to colonoscopy are needed. The colonoscopy capacity required will depend on the criteria. For example, in the U.K. FS trial, because of rather stringent criteria, only 5% of persons who underwent FS screening were referred for colonoscopy (Table 1).

Quality Assurance: Quality assurance is a central feature of organized cancer screening. If FS were to be integrated into provincial and territorial CRC screening programs quality assurance programs would be needed. A program would be required for the endoscopists, facilities, etc. A detailed assessment of what processes are currently in place would inform what needs to be added.

Monitoring and Evaluation: Information technology support and data systems would need to be developed to support the addition of FS to provincial and territorial CRC screening programs. There should be centralized capture of screening tests both within and outside of screening programs.

Issues Related to Non-Physician FS: In Ontario, to implement RN-FS three key specific issues had to be addressed:

1. Malpractice coverage for physicians when serving as trainers and when serving as a back up (following training, when RNs function independently).
2. Physician reimbursement during training and back-up phases (additional fee codes were added to the schedule of benefits).
3. Medical directives allowing RNs to perform FS at each participating hospital.

Cost-Effectiveness

The cost-effectiveness for all available screening modalities has not yet been established. However, there is a sense of cost-effectiveness based on modelled estimates. Most models use U.S. data to understand the cost of screening and cancer care. It must be kept in mind that any estimates of cost-effectiveness are strongly dependent upon:

- Risk of colorectal cancer in subjects eligible for screening.
- Frequency of screening examinations.
- Management of abnormal FS findings.
- Cost of a FS examination.

A systematic review of seven cost-effectiveness analyses of CRC screening methods (including one-time or annual FOBT, FS every five years and colonoscopy every 10 years) in average-risk persons conducted for the USPSTF concluded that:

- Screening for CRC is cost-effective compared with no screening (estimated cost between US$10,000 and $25,000 per life-year saved).
- A single optimal strategy could not be determined.[27]

A recent decision analysis also conducted for the USPSTF used the number of colonoscopies as a proxy for resource use (did not assess costs) and identified four strategies that provided similar life-years gained (assuming equally high adherence to screening):

1. Annual gFOBT screening with Hemoccult SENSA.
2. Annual screening with FIT.
3. FS every five years.
4. Colonoscopy every 10 years.[17]

Recently, two models that provide cost-effectiveness estimates for various screening modalities using Canadian costing data have been published; only one of these models included FS.

1. An economic analysis of FIT by the Canadian Agency for Drugs and Technology in Health (CADTH) concluded that a mid-sensitivity FIT was the most cost-effective strategy, being both less costly and more effective than a standard low-sensitivity gFOBT and colonoscopy.[25]
2. A model included FS as one of 10 screening strategies. It was determined that biennial low-sensitivity gFOBT, annual high-sensitivity FIT, annual FIT and colonoscopy every 10 years were the preferred strategies. It was estimated that FS every five years would result in fewer quality-adjusted life-years gained than did annual FIT, annual high-sensitivity FOBT or colonoscopy every 10 years. The incremental cost per quality-adjusted life-year gained, for a five-year period, with no screening was $6,192 for high-sensitivity FOBT, $6,237 for annual FIT and $7,892 for FS.[28]

Impact on Endoscopy Resources

Even given the substantial mortality reduction that FS screening could achieve, as reported by the FS trials, it will be a challenge for health systems to make any immediate changes to current approaches to screening. These systems may not have the capacity to accommodate immediate adoption of FS screening.

If policy decisions are made to allocate resources to FS screening, it will be necessary to ensure that adequate endoscopy capacity is maintained in the system to provide diagnostic services for symptomatic patients and for follow-up of those with positive FOBTs or FITs in a timely manner. This issue may be more prominent in shared endoscopy facilities, where both screening and diagnostic endoscopy is delivered.

The referral rates for colonoscopy resulting from FS screening in Canada would likely fall between rates reported from the NORCCAP trial (20.4%) and the U.K. FS trial (5.2%). For example, in a community-based FS clinic setting in Ontario, the observed referral rate to colonoscopy was 13%.[29] In addition, alternative models of service delivery should be considered, including screening in publicly funded, non-hospital settings.

An unintended consequence of publication of the FS trial results could be an increase the demand for colonoscopy by the public if there is a view that FS efficacy supports the likelihood of colonoscopy efficacy – even though the trials did not evaluate colonoscopy.

Another unintended consequence is that people are removed from further FS screening if they have an adenomatous polyp removed and they subsequently move on to surveillance colonoscopy, which requires additional colonoscopy resources.

If FS were integrated into existing and planned CRC screening programs, a suitable reimbursement and funding model would need to be developed.

Stakeholder Perspectives on Flexible Sigmoidoscopy Recommendations

Health-care providers, the public and patients will respond to FS recommendations based on past experience, knowledge, interpretation of the evidence and their own personal values and beliefs. Each group may advocate for their preferences.

Family Physicians: Family physicians may support FS because it provides more choice for patients. FPs may be concerned, though, that it will require more of their time to explain options, benefits and risks. FPs may view the added option of FS as providing relief on demands for colonoscopy, especially if their specialist colleagues endorse FS. FPs will likely be concerned about local access to FS, and will be influenced by the opinions of local specialists. FPs will need to be supported with clear information and direction about whether and how FS is to be introduced into CRC screening programs. Some FPs will consider whether there is a role for them in providing FS services.

Endoscopists: Gastroenterologists and general surgeons may be concerned that FS will encroach on colonoscopy resources but that colonoscopy will still be preferred because it is a more complete examination. They will be concerned about how the capacity for endoscopy can be increased through non-hospital models of delivery, with appropriate reimbursement methods for technical costs and equipment. If FS provided by non-physicians is an option, specialists may be concerned about compensation, liability and the possibility that colonoscopy could also be "taken over".

The Public and Patients: FS could be seen as an attractive screening option that is "more accurate" than FOBT yet entails less inconvenience and risk than colonoscopy. Physician recommendation will continue to influence the public. Patients who have been diagnosed with CRC by colonoscopy, and advocacy groups, may support FS, but may continue to promote colonoscopy as the "more accurate" test. If wait times for FS are perceived to be shorter than for colonoscopy, FS may be preferred. Once-in-a-lifetime screening is unlikely to resonate with the public and may be viewed as an attempt to save money. On the other hand, FS also provides one more option to increase the chance of CRC screening uptake.

Policy Implications

Given the evidence from the FS trials of the effectiveness of FS at reducing CRC incidence and mortality, public health officials and policy-makers will need to review and consider the potential implications for population screening strategies in their jurisdictions. As with all potential population screening tests, there will need to be evaluation of how FS meets key requirements for screening (below) and how it compares with FOBT and other screening tests.

Population screening strategies for any condition should be introduced only if certain requirements are met, as listed below.[30]

- The disease is an important public health problem.
- There is an effective treatment for localized disease.
- Facilities for further diagnosis and treatment are available.
- There is an identifiable latent or early-symptomatic stage of disease.
- The technique to be used for screening is effective.
- The test(s) are acceptable to the population.
- The natural history of the disease is known.
- There is a strategy for determining which patients should and should not be treated.
- The cost of screening is acceptable.
- Effective treatment is available and management of cases in the early stages has a favourable impact on prognosis.

Screening for CRC with gFOBT meets the above requirements. The results of the U.K. FS trial, and the PLCO trial show significant mortality benefit from one or two rounds of screening with FS. However, before making a decision to change current policies on CRC screening, the potential generalizability of FS trial results to the Canadian context (including uptake rates) will need to be considered.

Any policy changes adding FS as an option for CRC screening will require close monitoring and evaluation of the use of the test, best accomplished through phased implementation pilots with well-designed evaluation plans.

References

[1] Hol L, van Leerdam ME, Van BM, van Vuuren AJ, van DH, Reijerink JC, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. Gut 2010;59(1):62–8.

[2] Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ. 2009;338:b1846.

[3] Atkin WS, Edwards R, Wardle J, Northover JM, Sutton S, Hart AR, et al. Design of a multicentre randomised trial to evaluate flexible sigmoidoscopy in colorectal cancer screening. J Med Screen. 2001;8(3):137–44.

[4] Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JMA, Parkin DM, Wardle J, Duffy SW, Cuzick J. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomized controlled trial. Lancet. 2010;375(9726):1624-33.

[5] Segnan N, Senore C, Andreoni B, Aste H, Bonelli L, Crosta C, et al. Baseline findings of the Italian multicenter randomized controlled trial of "once-only sigmoidoscopy" – SCORE. J Natl Cancer Inst. 2002;94:1763–72.

[6] Segnan N, Armaroli P, Bonelli L, Risio M, Sciallero S, Zappa M, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian randomized controlled trial—SCORE. J Natl Cancer Inst. 2011;103(17):1310-22.

[7] Weissfeld JL, Schoen RE, Pinsky PF, Bresalier RS, Church T, Yurgalevitch S, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst. 2005;97:989–97.

[8] Schoen RE, Pinsky PF, Weissfeld JL, Yokochi LA, Church T, Laiyemo AO, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med. 2012;366:2345–57.

[9] Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med. 2000;343(22):1603–7.

[10] Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut. 2002;50(6):840–4.

[11] Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. Scand J Gastroenterol. 2004;39(9):846–51.

[12] Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. Br J Surg. 2008;95(8):1029–36.

[13] Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): an update. Am J Gastroenterol. 2008;103(6):1541–9.

[14] Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, Hemoccult. BMJ 1998;317(7158):559–65.

[15] Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365–71.

[16] Technical report for the national committee on colorectal cancer screening. Health Canada, 2002. Available from http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ncccs-cndcc/pdf/ccstechrep_e.pdf.

[17] Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, Van BM, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):659–69.

[18] Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med. 2004;351(26):2704–14.

[19] Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):638–58.

[20] Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps. 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008;58(3):130–60.

[21] van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology. 2008;135(1):82–90.

[22] Young GP, Cole SR. Which fecal occult blood test is best to screen for colorectal cancer? Nat Clin Pract Gastroenterol Hepatol. 2009;6(3):140–1.

[23] Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104(3):739–50.

[24] Zauber AG, Levin TR, Jaffe CC, Galen BA, Ransohoff DF, Brown ML. Implications of new colorectal cancer screening technologies for primary care practice. Med Care. 2008;46(9 Suppl 1):S138–S146.

[25] Heitman S, Au F, Hilsden R, Manns B. Fecal immunochemical testing in colorectal cancer screening of average risk individuals: economic evaluation. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

[26] Ho C, Jacobs P, Sandha G, Noorani HZ, Skidmore B. Non-physicians performing screening flexible sigmoidoscopy: clinical efficacy and cost-effectiveness [Technology report no. 60]. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2006.

[27] Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the US Preventive Services Task Force. Ann Intern Med. 2002;137:96–104.

[28] Telford JJ, Levy AR, Sambrook JE, Zou D, Enns RA. The cost-effectiveness of colorectal cancer screening in Canada. CMAJ. 2010;182(12):1283-4.

[29] Shapero TF, Hoover J, Paszat LF, Burgis E, Hsieh E, Rothwell DM, Rabeneck L. Colorectal cancer screening with nurse-performed flexible sigmoidoscopy: results from a Canadian community-based program. Gastrointest Endosc. 2007;65:640–5.

[30] Wilson JMG, Junger G. Principles and Practice of Screening for Disease. Geneva: WHO, 1968.