

# Screening Methods for Early Detection of Colorectal Cancers and Polyps

Summary of Evidence-Based Analyses

September 2009



Medical Advisory Secretariat  
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# List of Abbreviations

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<b>AUC</b>	Area under the curve
<b>BEIR</b>	Biological effect of ionizing radiation
<b>CI</b>	Confidence interval(s)
<b>CRC</b>	Colorectal cancer
<b>CT</b>	Computed tomographic
<b>CTC</b>	Computed tomographic colonography
<b>DCBE</b>	Double contrast barium enema
<b>FIT</b>	Fecal immunochemical test
<b>FOBT</b>	Fecal occult blood test
<b>FS</b>	Flexible sigmoidoscopy
<b>gFOBT</b>	Guaiac-based fecal occult blood test
<b>IAEA</b>	International Atomic Energy Agency
<b>ICRP</b>	International Commission on Radiological Protection
<b>iFOBT</b>	Immunochemical fecal occult blood test
<b>IY</b>	Incremental yield
<b>kVp</b>	Peak kilovoltage
<b>mA</b>	milliamperere
<b>MR</b>	Magnetic resonance
<b>mSv</b>	milli sievert
<b>OC</b>	Optical colonoscopy
<b>OR</b>	Odds ratio
<b>RCT</b>	Randomized controlled trial
<b>RR</b>	Relative risk
<b>SD</b>	Standard deviation
<b>SEER</b>	The Surveillance, Epidemology, and End Results
<b>SROC</b>	Summary receiver operating characteristic



# Background

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

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

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

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

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

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

## Objective

The objective of this review is to compare the diagnostic performance of various techniques for the identification of colorectal cancers and polyps in average risk people, 50 years of age and older in the context of colorectal cancer screening.

## Colorectal Cancer

The colon is a frequent site of carcinoma with colorectal cancer (CRC) being the third most common form of cancer and the second leading cause of cancer-related death in the Western world. When detected, the prognosis of CRC depends to a great extent upon the depth of tumour penetration into the bowel wall, regional lymph node involvement, and the presence of distant metastases. In practice, the Duke’s classification system is used to determine the extent of disease with the likelihood of 5-year survival of CRC patients depending closely on the Duke stage at the time of treatment (see Table 1).

Cancer of the colon generally spreads to regional lymph nodes or the liver via portal venous circulation. The liver is the most frequent site of metastatic dissemination; CRC rarely metastasizes to the lung, supraclavicular lymph nodes, bone, or brain without prior spread to the liver. A major exception to this occurs among patients in whom the primary tumour is located in the distal rectum. In these patients, tumours can readily spread to the lungs or supraclavicular lymph nodes without hepatic involvement. (1)

**Table 1: Modified Duke Classification of Colorectal Cancer**

Stage	Pathologic Description	Approximate 5-Year Survival Rate, %
A	Cancer limited to mucosa and submucosa	>90
B1	Cancer extends into muscularis	85
B2	Cancer extends into or through serosa	70–85
C	Cancer involves regional lymph nodes	30–60
D	Distant metastases are present (e.g., liver, lung)	5

Source: Isselbacher et al., Harrison's Principles of Internal Medicine. (1)

### Colonic Distribution

Many reports have indicated that there has been a shift in colonic distribution of colorectal cancers over the last 25 years. (2) An increased prevalence of right colonic tumors has been reported particularly among elderly patients. (3) Lieberman et al. (4) studied 3,196 individuals (including both average-risk and high-risk patients) recruited for screening and observed a trend toward an increased prevalence of advanced proximal neoplasia with age ( $P < .001$ ). The observed prevalence was 2% among patients 50 to 59 years old, 4.9% among those 60 to 69 years old, and 5.9% for those 70 to 75 years old.

Similarly, Obrand and Gordon (5) retrospectively reviewed the charts of 2,169 patients admitted to one hospital between 1979 and 1994 with a diagnosis of colorectal carcinoma. They reported that the right-sided colonic cancers steadily increased from 20.6% to 29.9% over the 16 years ( $P = .001$ ), whereas rectal cancers decreased from 22% over the first 4 years to 11.3% over the last study interval ( $P = .002$ ). In contrast, the frequency of transverse, left, and sigmoid colon lesions remained relatively unchanged. The authors suggested that an effective screening examination for carcinoma should include a complete examination of the colon.

### Incidence and Prevalence of CRC in Ontario

The incidence of CRC in Ontario is among the highest in the world (see Figure 1, page 11) with an estimated 8,000 new cases diagnosed in the province through 2008 (Canadian Cancer Society, Canadian Cancer Statistics, 2008). Over the same year, the disease is also estimated to have caused more than 3,250 deaths in the province, establishing it as a major public health concern (Figure 2). Examining the disease by age group, CRC is uncommon before age 50, after which it increases from 55 cases per 100,000 people in the 50 to 54 age group, to 423 cases per 100,000 in persons aged 85 and older. Correspondingly, disease mortality increases from 16 to 351 per 100,000 persons over the same age brackets (Figure 3).

## Colorectal Polyps

Colorectal polyps are one of the most common conditions affecting the colon and rectum. A colorectal polyp is a protrusion of the mucosal surface that occurs in the lumen of the colon or rectum. The majority of polyps are noncancerous and cause no symptoms. Of the various polyp types encountered in the colon, only neoplastic polyps are regarded as having malignant potential. Neoplastic polyps include tubular adenomas, villous adenomas, and villotubular adenomas (mixed adenomas). The most common form of non-neoplastic polyps are hyperplastic polyps, benign forms, which in most circumstances, are not considered to be premalignant.

### Characteristics

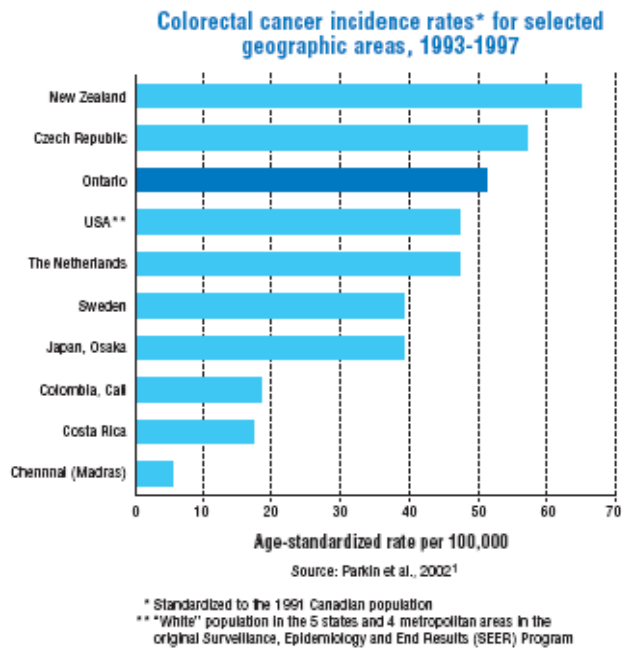
Colorectal polyps can be classified into three size categories:

- Small:  $\leq 5$  mm
- Medium: 6–9 mm
- Large:  $\geq 10$  mm

Polyps  $\geq 10$  mm in diameter are generally regarded as being clinically significant and those  $\leq 5$  mm in diameter as clinically insignificant as the majority of small polyps are of non-adenomatous type. The optimal threshold for screening may thus lie within the range of medium-to-large polyps.

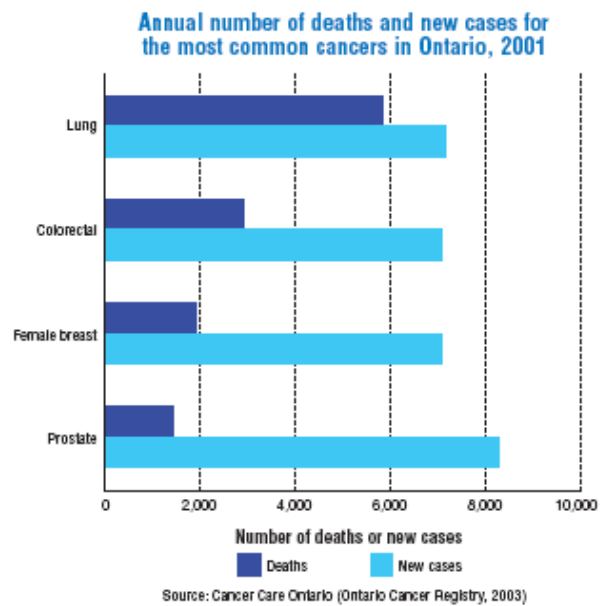
A polyp may be classified according to its morphology: pedunculated, sessile, or flat/depressed. The detection of large flat lesions is especially important, as these are more likely to become cancerous than a large polypoid lesion. (6) Though flat and depressed polyps appear to be common in Japan, some now believe that these polyps are more common among North Americans than previously thought. (7) Flat lesions do, however, remain difficult to detect and scientists in Japan have thus developed advanced methods for their detection during optical colonoscopy.

The least common form of neoplastic polyps are adenomas with a villous pathology, which, more often than others, are sessile in configuration. They have long been recognized as having the highest tendency toward malignant change. (8)



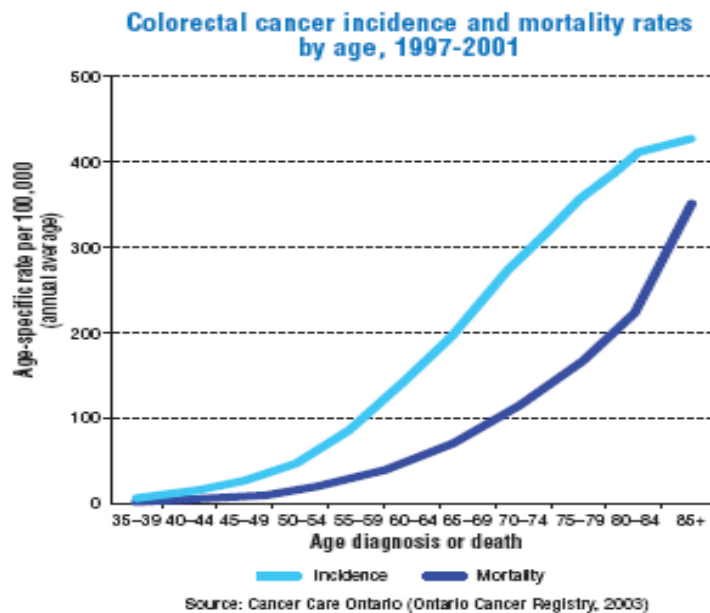
**Figure 1: Colorectal Cancer Incidence Rates for Selected Geographic Areas, 1993–1997**

Used with permission from Cancer Care Ontario and the Canadian Cancer Society. *Insight on Cancer. News and information on colorectal cancer.* Toronto: Canadian Cancer Society (Ontario Division), 2004



**Figure 2: Annual Number of Deaths and New Cases for the Most Common Cancers in Ontario, 2001**

Used with permission from Cancer Care Ontario and the Canadian Cancer Society. *Insight on Cancer. News and information on colorectal cancer.* Toronto: Canadian Cancer Society (Ontario Division), 2004



**Figure 3: Colorectal Cancer Incidence and Mortality Rates in Ontario by Age, 1997–2001**

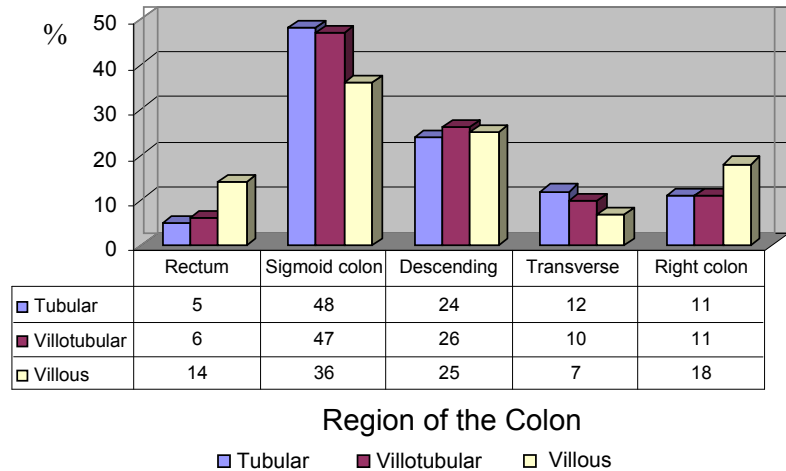
Used with permission from Cancer Care Ontario and the Canadian Cancer Society. *Insight on Cancer. News and information on colorectal cancer.* Toronto: Canadian Cancer Society (Ontario Division), 2004

## Prevalence

According to Pickhardt et al. (9), large adenomatous polyps are seen in 3.9% of asymptomatic people, 50 years of age and older, while adenomatous polyps 6 mm or larger are seen in 13.6% of this group.

## Colonic Distribution

Shinya et al. (8) analyzed a series of 5,786 adenomas from over 7,000 endoscopically removed polyps. Each form of adenoma (tubular, villous, villotubular) occurred more frequently in the sigmoid colon, followed by the descending colon. This finding is in line with the results of several studies, which reported the association of sigmoidoscopy and reduced mortality from CRC (Figure 4).



**Figure 4: Distribution of Types of Adenomas**

Source: Shinya and Wolff, 1979. (8)

## Transformation to Cancer

The majority of CRCs are believed to arise from asymptomatic adenomatous polyps, which have been shown to take about 10 years to transform into invasive CRC. This leaves a substantial window of opportunity in which to find and remove these precancerous polyps before they become malignant.

In a rigorous test of the hypothesis that polypectomy via colonoscopy can reduce the incidence of CRC, The National Polyp Study demonstrated that polypectomy could reduce CRC incidence by as much as 76%. (10) The study cohort consisted of 1,418 patients (mean age of  $61 \pm 10$  years) who had undergone complete colonoscopy, during which one or more adenomas of the colon or rectum were removed. At the time of enrolment, 494 patients (35%) had adenomas  $\geq 10$  mm in diameter and 137 (10%) had adenomas with high-grade dysplasia. Patients underwent periodic colonoscopy with an average follow-up of 5.9 years. The incidence of CRC in the patient cohort was compared with that of three reference groups:

- The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, which represents people at average risk in the United States.
- Data from Mayo Clinic in the United States (1965-1970) consisting of patients in whom a colorectal polyp  $\geq 10$  mm or larger, beyond the reach of a rigid sigmoidoscope, was detected by barium enema. Polypectomy was not performed in these patients as they declined such intervention.
- Data from St. Mark's Hospital in the United Kingdom (1957-1980) consisting of patients from whom a rectosigmoid adenomatous polyp was removed.

The results of the study showed that during follow-up, asymptomatic CRC was detected in five patients. No symptomatic cancer was found and none of the patients died of CRC. The observed incidence of CRC

in the study cohort was significantly lower than expected ( $P < .001$ ) based on the rates found in the three reference groups. Specifically, the observed incidence per 1,000 person-years was 0.6 in the study cohort, compared with the expected incidence of 2.5 in the SEER group, 5.8 in the Mayo Clinic group, and 5.2 in the St. Mark's Hospital group. The percentage reduction in CRC incidence was 76% compared with SEER data ( $P < 001$ ), 90% compared with Mayo Clinic data, and 88% compared with St. Mark's Hospital data. The study thus provided evidence of the progression of adenoma to carcinoma, as well as evidence that the incidence of CRC can be reduced by colonoscopic polypectomy.

## **Average versus High Risk for Colorectal Cancer**

Persons in whom age is the only risk factor for CRC are considered to be at average risk. Factors that place individuals at higher risk include a family history of CRC or adenoma, personal history of CRC or adenoma, and inflammatory bowel disease. (11;11) There is mounting evidence endorsing the provision of CRC screening to average-risk individuals, beginning at age 50, to detect cancers at a favourable stage before they have advanced to a potentially lethal disease state. The introduction of a method to identify high-risk patients would allow for their prompt diagnosis and treatment and further reduce the burden of the disease in Ontario. For those at high risk, screening beginning at an earlier age may be reasonable; however, such a consideration is beyond the scope of this review.

## **Colorectal Cancer Screening**

The objective of CRC screening is to reduce the burden of CRC and thereby the morbidity and mortality rate of the disease. It is believed that this can be achieved by regularly screening the average-risk population, enabling the detection of cancer at early and curable stages and polyps before they become cancerous. Several methods of screening for CRC have been proposed by various organizations, each with their own advantages and drawbacks. It should be kept in mind, however, that no infallible technique exists and there is a need for continued improvement in screening methods. As with other screening tests, the ideal screening technique for CRC should be feasible, accurate, safe, acceptable, and cost-effective.

### **Optical Colonoscopy**

Colonoscopy is currently the gold standard for the detection of colorectal neoplasia, yet its true sensitivity is difficult to determine. One needs to remember that the success of the technique in identification of colorectal lesions is highly dependent on the skills of the endoscopist. The initial measures of sensitivity of colonoscopy for adenomas were made by tandem colonoscopy studies. (12;13) Rex et al. (12) determined miss rate of colonoscopy using same day, back-to-back colonoscopies. The miss rate was shown to be 13% for adenomas 6-9 mm and 6% for adenomas  $\geq 10$  mm. Right colon adenomas were missed more often (27%) than left colon adenomas (21%), but the difference was not statistically significant. Hixson et al. (13) studied the colonoscopic miss rate in a blinded trial. In this study colonoscopy did not miss any of the 63 lesions 10 mm or larger while 12% of the 6-9 mm lesions were missed.

More recently, the technique of segmental unblinding in CT colonography studies has been used to demonstrate the true sensitivity of colonoscopy for detection of adenomas. However, this technique is not a reliable method for determination of sensitivity of colonoscopy for polyps less than 10 mm in size. Pickhardt et al. (9) used the technique of segmental unblinding and reported that colonoscopy had a higher sensitivity for detection of patients with adenomas 6 mm and larger (90%) than that for detection of patients with adenomas 10 mm or larger (88%).

The interior lining of the colon from anus to cecum can be visualized through colonoscopy, allowing for a high rate of detection of potentially curable CRCs and precancerous adenomatous polyps. The advantage

of colonoscopy is that it allows detection, biopsy, and removal of the lesions identified. Therefore, a single session detection and treatment would be more convenient for the patients. In addition, longer interval for repeat screening has the potential to minimize the costs associated with two stage screening with other tests.

The technique will, however, fail to visualize the cecum in 5% to 10% of average-risk people due a variety of reasons, such as tortuosity or malrotation of the loops, bowel spasm, diverticulitis or diverticulosis, ischemic colitis, colonic configuration due to previous surgery, obstructive tumors, external compression from masses or hernia. (14)

Colonoscopy is also an invasive technique associated with clinically important complications such as bleeding and perforation (although these risks are small and are more commonly associated with polypectomy and/or biopsy). (15) A study conducted among the United States Medicare population examined the risk of colonic perforation following colonoscopy and sigmoidoscopy. (16) Overall, there were 77 perforations after 39,286 colonoscopies (incidence = 1.96/1,000 procedure). The risk of perforation for those who underwent screening colonoscopy (n = 20,163) was 1.3/1,000. Likewise, a large Swedish study involving 6,066 diagnostic and therapeutic colonoscopies demonstrated that bleeding and perforation occurred in 0.2% and 0.1% respectively with no colonoscopy related mortality. (17) Bleeding was confined to therapeutic colonoscopy and occurred immediately – mainly after removal of large polyps with thick stalks. Perforation during diagnostic colonoscopy occurred in the left colon and was diagnosed sooner than perforations due to therapeutic colonoscopy, which more frequently occurred in the cecum. The bleeding was correlated to the experience of endoscopist.

The risk of perforation is higher in the presence of conditions such as active colitis, inflammation, diverticular or ischemic disease, and prior irradiation. Although colonoscopy is not routinely indicated for patients with inflammatory bowel disease, it may be indicated for patients with ulcerative colitis of more than 10 years' duration because of an increased risk of carcinoma.

Though there are no published randomized trials, there is indirect evidence that colonoscopy can reduce the overall incidence and mortality of CRC. The technique was an integral part of the FOBT clinical trials that demonstrated reduction in mortality through colorectal cancer screening.

Colonoscopy and other techniques for CRC screening can be classified according to three categories:

Endoscopic techniques:

- Optical colonoscopy
- Flexible sigmoidoscopy (FS)

Stool-based techniques:

- Fecal occult blood test (FOBT)
- Fecal Immunochemical Test (FIT)
- Fecal DNA testing

Imaging techniques:

- Virtual colonoscopy techniques using:
  - a) Computed tomographic colonography (CT colonography)
  - b) Magnetic resonance colonography (MR colonography)
- Wireless capsule endoscopy (PillCam Colon)
- Double-contrast barium enema (DCBE)

# Evidence-Based Analysis of Effectiveness

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## Research Question

Which screening method results in a greater reduction in CRC incidence and mortality?

What is the accuracy of the screening tests in detection of CRC and polyps in individuals 50 years of age and older compared with the gold standard of optical colonoscopy?

How safe are CRC screening tests in the context of general population screening?

## Primary Outcomes

- The relative risk of dying from CRC (screening test vs. no screen, or screening test vs. gold standard)
- The sensitivity or diagnostic yield of each method for CRC identification in patients aged  $\geq 50$  years
- The sensitivity or diagnostic yield of each method for the identification of colorectal polyps (adenomatous type) in patients aged  $\geq 50$  years

## Methods

The following CRC screening tests were considered for evaluation:

- computed tomographic colonography (CT colonography)
- magnetic resonance colonography (MR colonography)
- wireless capsule endoscopy (PillCam Colon)
- fecal occult blood test (FOBT)
- flexible sigmoidoscopy (FS)

## Inclusion Criteria

- prospective studies reporting on mortality from CRC using any screening method
- prospective studies comparing test accuracy with optical colonoscopy for CRC and polyp detection
- studies reporting results in absolute numbers

## Exclusion Criteria

- retrospective studies
- studies of anatomical areas other than the colon
- studies addressing other diseases of the colon
- studies addressing technical, educational, or other aspects of the selected tests
- studies that did not report accuracy data

## Data Analysis

A meta-analysis was carried out to analyze the results of the trials containing mortality data and those trials in which the diagnostic accuracy of the tests was reported. Summary receiver operating characteristic (SROC) methodology was used as a measure of accuracy for CT colonography and MR colonography where per-patient data were reported. Pooled sensitivities and specificities, as well as 95% confidence intervals (CI) were calculated for per-polyp analyses. For some specific outcomes, odds ratio (OR) and 95% CI, or other descriptive statistics were used to demonstrate the effect size.



## Results of Literature Search

A search of electronic databases including OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, The Cochrane Library, and the International Agency for Health Technology Assessment (INAHTA/CRD) database was undertaken for each test under review. The search was limited to English-language articles and human studies (as detailed in Appendices 1 to 4). The search dates were as follows:

- CT colonography: January 1, 2003 to January 30, 2008
- MR colonography: January 1, 2003 to January 30, 2008
- PillCam Colon: January 1, 2003 to July 20, 2008
- FOBT: January 2003 to June 2008
- FS: January 1, 2004 to July 31, 2008

Since two CT colonography studies on average risk people became published after our search date, this report was updated in July 2009 to include their results. Overall, 60 studies and six systematic reviews on FOBT met the inclusion criteria (see Tables 2 and 3).

**Table 2: Quality of Evidence of Included Studies Reporting Diagnostic Accuracy as End Point**

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT, Systematic review of RCTs	1	1
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	55
Non-RCT with historical controls	3b	1
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	0

CT indicates computed tomographic; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; g, grey literature; MR, magnetic resonance; RCT, randomized controlled trial.

**Table 3: Quality of Evidence of Included Studies (Studies Reported Mortality as End Point)**

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

FOBT indicates fecal occult blood test; g, grey literature; RCT, randomized controlled trial.

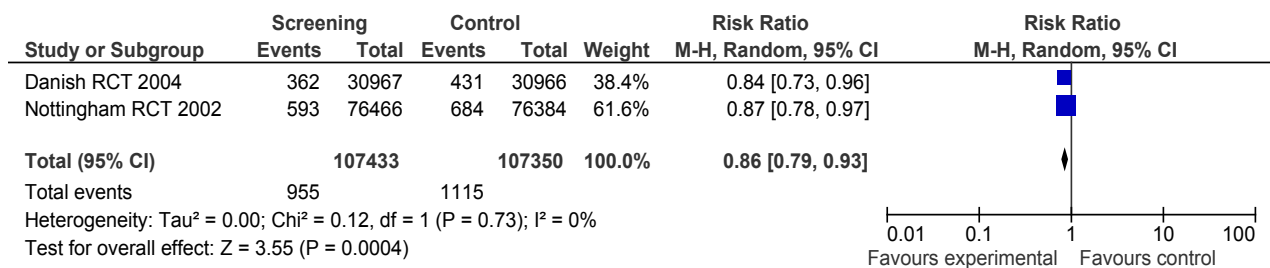
# Results of Evidence-Based Analysis

## Studies on Average Risk People

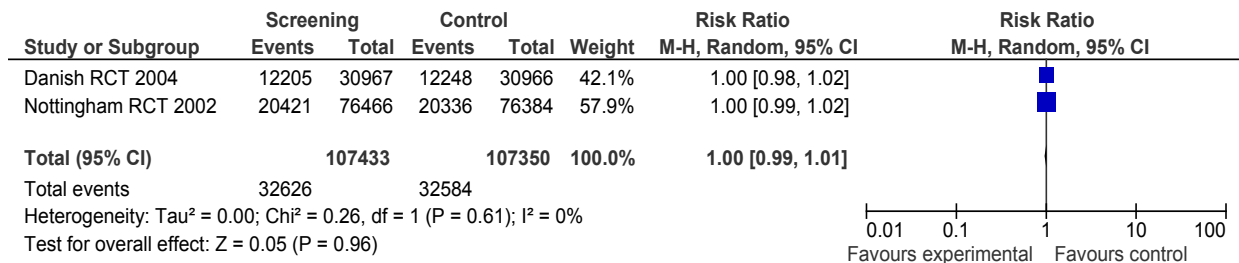
### Studies with Mortality Outcomes

Three randomized population-based studies have shown that screening for CRC using guaiac-based FOBT (gFOBT) can reduce CRC mortality. (18-20) A meta-analysis was conducted to summarize the results of the two studies in which non-rehydrated gFOBT was used. (18;19) The third study, the Minnesota trial (20), was excluded from this analysis as it used rehydrated gFOBT. The combined results of the Danish and Nottingham trials showed a 14% relative risk reduction in CRC mortality (RR 0.86; 95% CI, 0.79–0.93), as displayed in Figure 5. No significant differences were observed in all-cause mortality (see Figure 6).

Sensitivity, specificity, and the positive predictive value of gFOBT were estimated in the RCTs as not all participants were offered colonoscopy. In these studies, only those people with a positive gFOBT were offered a follow-up colonoscopy evaluation. Furthermore, the number of false negatives could not be calculated as those participants with a negative gFOBT did not have their test results confirmed via colonoscopy. A summary of the sensitivities and specificities calculated by The Canadian Task Force on Preventive Health Care (21) is shown in Table 4.



**Figure 5: CRC Mortality: Biennial Nonrehydrated gFOBT Compared With Control Groups**



**Figure 6: All-Cause Mortality: Biennial Nonrehydrated gFOBT Compared With Control Groups**

**Table 4: Sensitivity of gFOBT for Detection of Colorectal Cancer in Biennial Screening**

RCT	Follow-up, years	Sensitivity for Cancer, %
Nottingham trial	10	54
Danish trial	10	45

gFOBT refers to guaiac-based fecal occult blood test; RCT, randomized controlled trial.

In a review by Rabeneck et al. (22), 13 prospective studies provided data on performance characteristics of a one time application of gFOBT in an asymptomatic population. In 3 of the 13 studies, colonoscopies were performed on all subjects regardless of the FOBT results, allowing for the determination of sensitivity and specificity of gFOBT. However, one of these studies used rehydrated FOBT. The diagnostic performance of gFOBT in the two studies of nonrehydrated gFOBT are shown in Table 5.

**Table 5: Sensitivity of gFOBT for Detection of Colorectal Cancer in Single Testing Trials**

Study, Year	N	Test			Positive Predictive Value, %
		Positivity, %	Sensitivity, %	Specificity, %	
Imperiale et al., 2004	4,404	10.8	12.9	95.2	5.5
Sung et al., 2003	505	20.0	25.0	80.0	1.0

gFOBT indicates guaiac-based fecal occult blood test; N, number of subjects.

Adapted from Rabeneck et al. (22)

Six cohort studies (23-27;27-29) reported on sensitivity and specificity of iFOBT for CRC detection. Three of these (24;25;29) also reported sensitivity of iFOBT for detection of adenomas  $\geq 10$  mm in diameter. There was significant heterogeneity in the reported sensitivities and specificities. Specifically, the pooled sensitivity of iFOBT for the detection of adenomas  $\geq 10$  mm was 0.28 (95% CI, 0.19–0.37) and the pooled specificity of iFOBT for the detection of adenomas  $\geq 10$  mm was 0.91, (95% CI, 0.90–0.92). Table 6 shows the pooled sensitivity and specificity of iFOBT for detection of cancers as well as polyps  $\geq 10$  mm in diameter. One cohort study (30) (N=8,104) directly evaluated gFOBT with iFOBT using colonoscopy as the reference standard (Table 7).

**Table 6: Pooled Sensitivity of iFOBT for Detection of Colorectal Cancer and Large Adenomas**

Test	Sensitivity	Specificity
Detection of cancer	0.81 (95% CI, 0.74–0.87)	0.94 (95% CI, 0.94–0.95)
Detection of adenomas $\geq 10$ mm	0.28 (95% CI, 0.19–0.37)	0.91 (95% CI, 0.90–0.92)

CI refers confidence interval; iFOBT, immunochemical fecal occult blood test.

**Table 7: Comparison of the Sensitivity of iFOBT Versus gFOBT for Detection of Colorectal Cancer and Large Adenomas**

Test	Sensitivity for Cancer, %	Sensitivity for Polyps $\geq$ 10 mm, %
gFOBT	37.1 (95% CI, 19.7–54.6)	30.8 (95% CI, 21.6–40.1)
iFOBT	68.8 (95% CI, 51.1–86.4)	66.7 (95% CI, 57.0–76.3)

CI refers to confidence interval; gFOBT, guaiac-based fecal occult blood test; iFOBT, immunochemical fecal occult blood test.

### Studies with Diagnostic Outcomes

Five studies including two RCTs (one large and one small) (16;31) and two prospective cohort studies (one large and one small) (32-34) reported diagnostic outcomes of several techniques for the identification of CRCs and adenomatous polyps. Generally, in these studies, advanced adenomas were defined as an adenoma with any of the following features:

- a villous component greater than 20%,
- high-grade dysplasia,
- size  $\geq$ 10 mm in diameter.

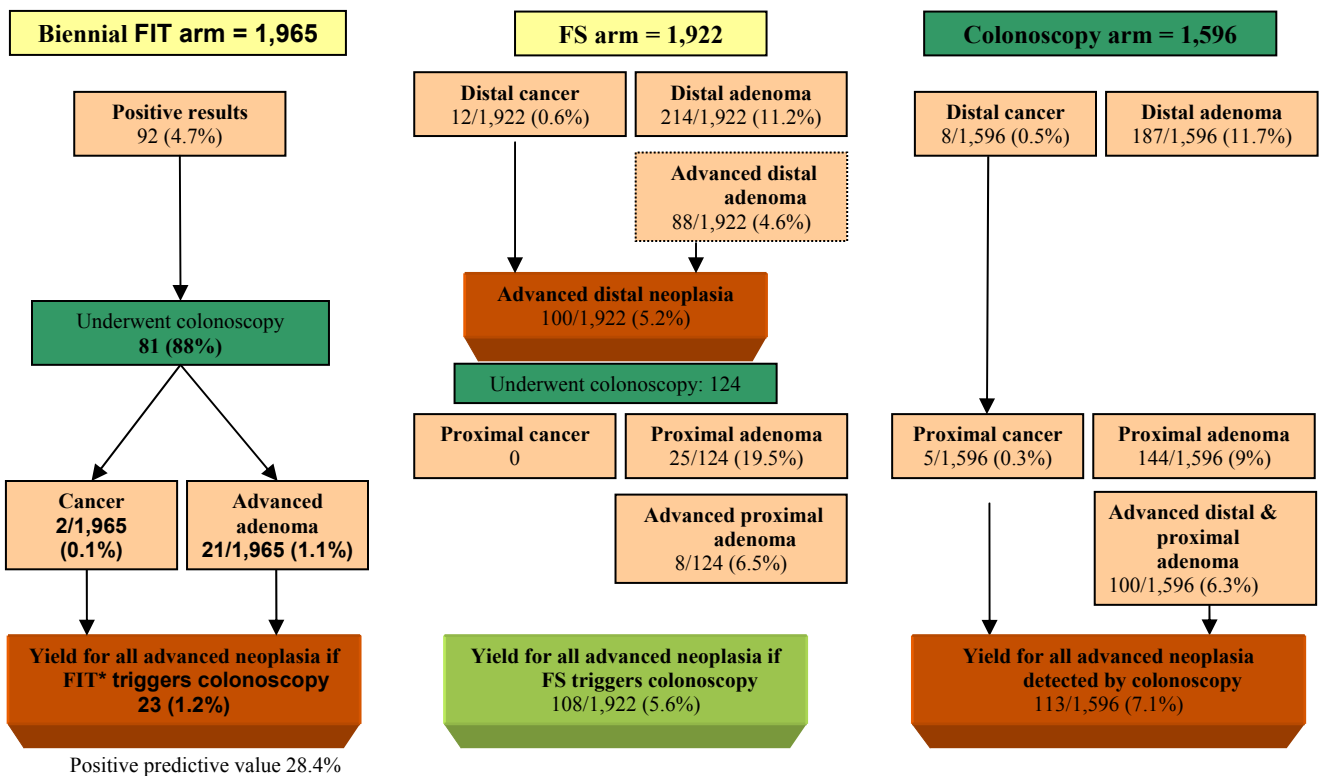
Advanced neoplasia was defined as cancer and/or advanced adenoma.

### Randomized Controlled Trials

Two RCTs (16;31) compared the yield of several techniques for the identification of CRC. A large population-based multicentre randomized trial conducted across six centres in Italy (SCORE3 trial) (16) compared three methods of CRC screening: once-only FS, once-only colonoscopy, and biennial fecal immunochemical test (FIT). The objective of the study was to assess the attendance and compare the detection rate and acceptability of different CRC screening strategies. A total of 18,114 people participated in the study, of which 5,483 were analyzed. The reported diagnostic yields of the three screening strategies are summarized in Figure 7.

Advanced neoplasia was detected in 1.2% of those persons in the FIT arm, 5.2% of those in the FS arm, and in 7.1% of the colonoscopy arm. A 42% increase in detection rate was observed in the colonoscopy arm compared with the FS arm after adjusting by age, gender, and screening centre (OR, 1.42; 95% CI, 1.08–1.88). This gain in detection rate was explained by a marked increase in the detection of advanced neoplasia among people aged 60 years and over (OR, 2.00; 95% CI, 1.30–3.09). The detection rate was not different between the FS and colonoscopy arms for people younger than 60 years (OR, 1.08; 95% CI, 0.74–1.57). The detection rate for advanced neoplasia in the distal colon was the same for the FS and colonoscopy arms (OR, 1.02; (95% CI, 0.75–1.37). In comparison, detection rate was markedly lower in the biennial FIT arm compared with the FS arm (OR, 0.22; 95% CI, 0.14–0.35) as shown in Table 8.

Based on the observed prevalence of advanced adenomas in the FS and colonoscopy arms, it was estimated that screening by FS would result in identification of 72% of people with advanced neoplasia.



FIT indicates immunochemical FOBT; FS, flexible sigmoidoscopy.

**Figure 7: Yield of Three Colorectal Cancer Screening Strategies**

**Table 8: Comparison of Three Colorectal Cancer Screening Strategies**

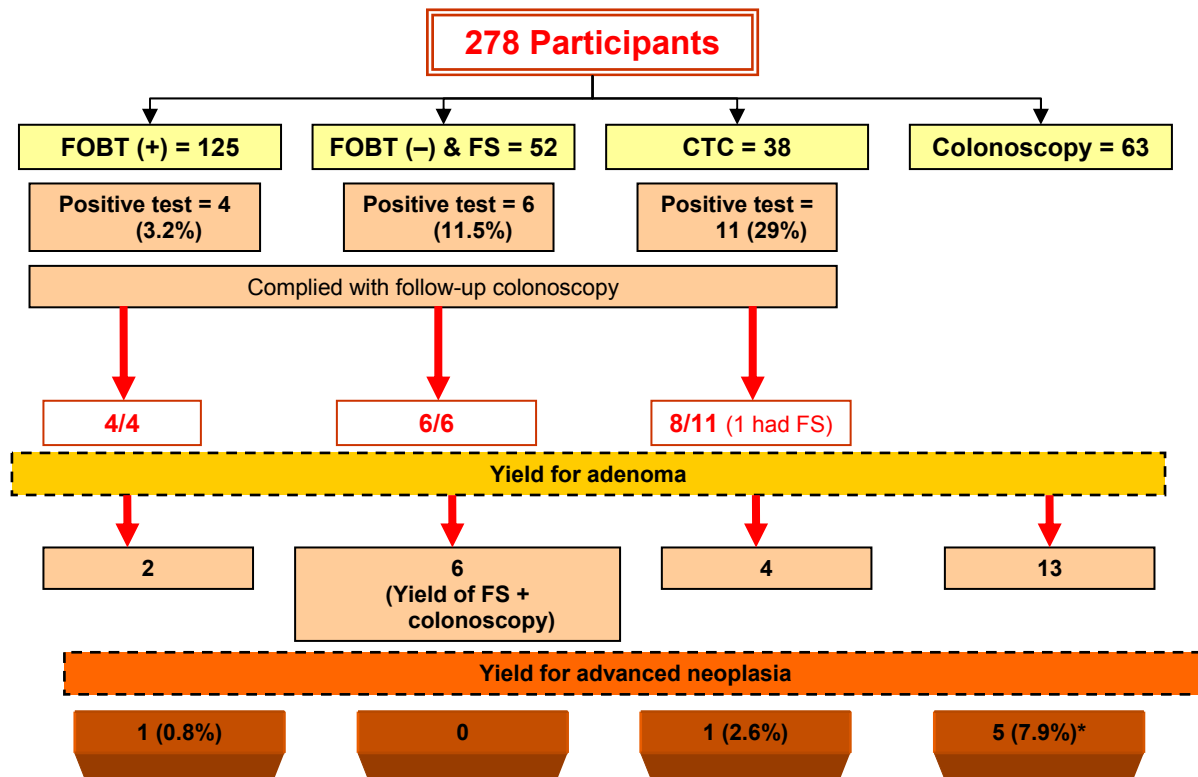
Screening Test	Detection Rates, %		
	Cancer	Advanced Adenomas	Advanced Neoplasia
FS (n=1,922)	0.6	4.6	5.2
Biennial FIT (n=1,965)	0.1	1.1	1.2 (OR, 0.22 [95% CI, 0.14–0.35]†)
Colonoscopy (n=1,596)	0.8	6.3	7.1 (OR, 1.42 [95% CI, 1.08–1.88]†)

CI refers to confidence interval; FIT, immunologic fecal occult blood test; FS, flexible sigmoidoscopy; OR, odds ratio.

†Compared with FS.

A second randomized comparative study conducted in Australia compared the participation rates, yield of advanced colorectal neoplasia, acceptabilities, and safety of six different screening strategies (FOBT, FOBT<sup>(-)</sup> + FS, CT colonography, colonoscopy, and a choice of screening with two different options). (31) A total of 1,679 people aged 50 to 54, or 65 to 69 years, were randomly selected from the electoral roll, of

which 1,333 people were considered eligible and 278 eventually screened (20.9%, [95% CI, 18.7%–23.1%]). Figure 8 shows the yield for cancer and advanced adenomas in this study. The results showed that the highest yield for advanced neoplasia was in participants having colonoscopy at 7.9%. The yields in the CTC and FOBT groups were 2.6% and 0.8%, respectively (see Table 9). The positivity rate of the test was 11.5% for FS & FOBT and 29% for CT colonography and thirteen adenomas were detected in 63 participants undergoing colonoscopy.



*P* = 0.02 compared with FOBT

CTC indicates computed tomographic colonography; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy.

**Figure 8: The Multicentre Australian Colorectal Neoplasia Screening (MACS) Study**

**Table 9: Yield of Different Colorectal Cancer Screening Strategies**

Screening Test	Participants	Positive Test, n	Negative Test, n	Complied With Follow-up Colonoscopy, n	Adenoma, n	Number With Advanced Colorectal Neoplasia, n (Yield)
FOBT	125	4	121	4	2	1 (0.8%)
FOBT/FS	52	6	46	6	6†	0
CTC	38	11	27	8 (1 had FS)	4	1 (2.6%)
Colonoscopy	63	na	na	na	13	5 (7.9%); <i>P</i> = .02 (compared with FOBT)

CTC refers to computed tomography colonography ; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; na, not applicable. †Yield at FS+colonoscopy.

## Prospective Cohort Studies

Two prospective cohort studies compared the yield of several techniques for the identification of CRC and advanced colorectal adenomas, the American College of Radiology Imaging Network (ACRIN) Multicentre Study and a German study by Graser et al., 2009. (32;33)

### *American College of Radiology Imaging Network (ACRIN) Multicentre Study*

Johnson et al. (32), conducted a large multicentre study in which 2,600 asymptomatic people 50 years of age and older were recruited through 15 clinical sites. Participants were scheduled to undergo routine colonoscopy at the participating sites between February 2005 and December 2006. Patients underwent both CT colonography and colonoscopy. Complete CT examination and colonoscopy results were available for 2,531 (97%) participants. The majority of them had no known risk factors for CRC, other than the age. Nine percent of the participants had a first degree relative with a history of colorectal polyp or cancer, 1% had personal history of polyp or cancer, and less than 1% had both. All others were considered to be at average risk for CRC. The mean age of the participants was 58.3 years and 48% were male.

The preparation for CT colonography included standard bowel purgation and the use of fluid and stool tagging. All examinations were performed with multidetector scanners (64- slice in 1,308, 40-slice in 83, and 16-slice in 1,140 patients) in both supine and prone positioning. Images were acquired with collimation of 0.5-1 mm, 50 mAs effective dose and a peak voltage of 120 kV. Images were reconstructed to slice thickness of 1-1.25 mm with a reconstruction interval of 0.8 mm. Images were randomly read using either primary 2D image display with 3D for problem solving (n=1280), or a primary 3D endoluminal fly through with 2D for problem solving (n=1,251). The radiologists made their interpretations without knowledge of colonoscopy results and were instructed to record only lesions measuring 5 cm or more.

Same day CT colonography and colonoscopy examinations were performed in 99% of the participants. Each participating radiologist had experience of at least 500 CT colonography examinations or had participated in specialized 1.5 day training session in CT colonography. In addition, all were required to complete a qualifying examination in which they achieved a detection rate of 90% or more for polyps measuring 10 mm or more in a reference image set. Of 20 radiologists who initially met entry criteria, 15 with the highest scores were invited to participate in the study. All colonoscopy examinations were performed or directly supervised by an experienced endoscopist without knowledge of CT colonography results. If a lesion 10 mm or more was detected by CT colonography but not by colonoscopy, patients were advised to undergo a second colonoscopy within 90 days. The endoscopists performing the second colonoscopy were aware of the results of CT colonography.

Ten of the 2,531 participants did not have colonoscopy data documented to the cecum because of previous resection. A total of 547 lesions measuring 5 mm or more were detected. There were 128 large adenomas ( $\geq 10$  mm) or carcinomas in 109 of the 2,531 participants (prevalence of 4.3%). Seven adenocarcinomas 10 mm or more in diameter were detected in seven patients. Non-adenomatous lesions included hyperplastic polyps (n= 136), lipoma (n=7), or other types (n=30). A total of 2.4% of patients had a flat lesion (height/weight ratio  $\leq 50\%$ )

The sensitivity, specificity, positive predictive value, and negative predictive values were similar for participants at increased risk for CRC and for those at average risk of CRC. The sensitivity of CT colonography for the detection of large polyps ranged from 67% to 100% among radiologists with 7 of 15 radiologists correctly identifying all those patients in whom there were large lesions. The pooled sensitivities for detection of large lesions were similar for primary 2D and primary 3D. CT colonography



missed a single 10 mm cancer in the low rectum, which was not found to be visible on a second CT review (sensitivity for cancer, 85.7%). Overall, CT colonography detected 90% of large and 78% of medium-to-large adenomas or cancers.

Table 6 shows sensitivity, specificity, and area under the ROC curve for detection of patients with large and medium-to-large adenomas and cancers. However, for the detection of patients with large lesions ( $\geq 9$  mm) regardless of histological type the sensitivity, specificity and AUC were  $87\% \pm 3.5\%$ ,  $86\% \pm 2.2\%$ , and  $88\% \pm 2\%$ . A specificity of 86% for large lesions translates to a false positive rate of 14%. The sensitivity of CT colonography for detection of adenomas/cancers is shown in Table 10.

**Table 10: Sensitivity and Specificity of CT Colonography For Detection of Patients With Adenomas and Cancers**

$\geq 9$ mm			$\geq 6$ mm		
Sensitivity % (95% CI)	Specificity % (95% CI)	AUC % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC % (95% CI)
90 (83-96)	86 (81.7-90.2)	89 (85-93)	78 (71-85)	88 (84-92)	84 (81-88)

AUC, Area under curve

Sensitivity of CT colonography for detection of cancers and large adenomas ( $> 9$  mm) or cancers and medium-to-large adenomas ( $\geq 6$  mm) was  $82 \pm 0.04$  and  $70 \pm 0.05$  respectively. A total of 30 lesions 10 mm or larger in 27 patients were detected by CT colonography but not by colonoscopy. Fifteen of these people with 18 lesions underwent a repeat colonoscopy and 5 of the 18 lesions were confirmed.

Three adverse events were reported by the study centres. One person developed severe nausea and vomiting after CT colonography, which lasted less than 24 hours. Hematochezia occurred in one patient after snare polypectomy requiring 2 days hospitalization. Bacteremia with *Escherichia coli* occurred in one patient 24 hours after both procedures.

Extracolonic findings were observed in 1,670 people (66%) and 405 (16%) were deemed to require additional evaluation or urgent care. The findings were in the chest (27%), genitourinary tract (45%), GI tract (18%), and musculoskeletal system (3%).

### ***Graser et al., 2009***

Graser et al. (33) was a prospective trial designed to compare the performance characteristics of five different screening tests for the detection of advanced colonic neoplasia in average risk people. Five different screening were compared for the same patients: CT colonography, colonoscopy, flexible sigmoidoscopy, fecal immunochemical stool testing, and FOBT. Separate sigmoidoscopies were not performed and the results from endoscopic examination of rectum and sigmoid colon were used to show the performance of FS. The study was powered to detect a 10% difference in colonoscopy and CT colonography sensitivity for detection of polyps  $> 5$  mm. The authors did not report how the study population was recruited but it was stated that a total of 311 consecutively enrolled people, 50-81 years of age (mean age 60.5), of which 171 were men, were included in the study.

All polyps were resected or biopsied and sent for histopathological examination. Overall, 511 lesions were detected, of which, 418 were  $\leq 5$  mm, 56 were 6-9 mm, and 37 were  $> 9$  mm. Of all polyps detected, 221 (43.2%) were adenomatous and 290 (56.8%) were non-adenomatous. A total of 248 (48.6%) of these

were located within the reach of FS (78 adenomatous and 170 non-adenomatous). The study did not report on the results of segmental unblinding. From the data presented in Table 3 of the report, however it seems that one adenoma in the 6-9 mm size range was missed by colonoscopy. Table 11 summarizes the reported sensitivities for CT colonography and colonoscopy for detection of colonic adenomas in the study.

**Table 11: Sensitivity of CT Colonography and Optical Colonoscopy for Detection of Colonic Adenomas**

Sensitivity % (95% CI)				
	>9 mm	6-9 mm	≤5 mm	All sizes
OC	100 (89.4-100)	92.7 (80.1-98.5)	94.6 (89.6-97.6)	95.9 (92.4-98.1)
CTC	93.9 (79.8-99.3)	90.2 (76.9-97.3)	59.2 (50.8-67.2)	70.1 (63.8-76.1)

The prevalence of large adenomas (> 9 mm) in this study was 8.1% (25/307), twice of that found in Johnson’s study. This rate was also twice of that in another large study by Pickhardt et al. (9) in which only asymptomatic people were included. Therefore, the generalizability of the results of this study to the screening populations in which the prevalence of large adenomas are much lower is questionable.

In Graser’s study, colonoscopy reached the highest sensitivities for detection of patients with adenomas (100% of patients with adenomas 10 mm or larger, 97.8% of patients with adenomas 6 mm or larger, and 97.3% of patients with adenomas of all size categories). CT colonography was the next most sensitive technique in identifying patients with adenomas (92% of patients with adenomas 10 mm or larger and 91.3% of patients with adenomas 6 mm or larger). Flexible sigmoidoscopy had a sensitivity of 68% and 67% for detection of patients with adenomas 10 mm or larger and 6 mm or larger respectively. The sensitivity and specificity of the different screening tests (alone and in combination) for the detection of patients with colonic adenomas are shown in Table 12.

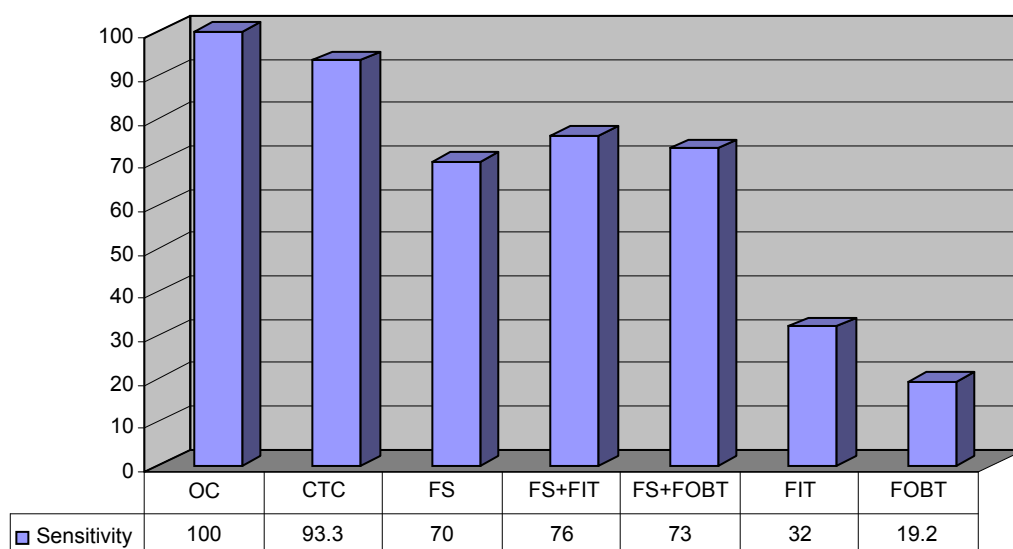
This study also reported on detection of advanced neoplasia. Forty-six advanced lesions were detected among 30 patients, from which 33 were ≥10 mm, six were 6-9 mm, and seven were ≤5 mm or smaller. The largest advanced lesion was a 57 mm stage 3 carcinoma of the transverse colon. This lesion was identified by CT colonography, colonoscopy, FIT, and FOBT, but not by FS as it was out of reach of the sigmoidoscope. Colonoscopy identified all the advanced neoplasias, while CT colonography missed one 16 mm, one 10 mm, and one 4 mm lesion with a villous component. The patient with a 4 mm advanced lesion, however, also had two other lesions 14 mm and 11 mm in size. The patient would thus have been detected by CT colonography, while the other two patients would have remained undetected. The overall sensitivity of CT colonography and colonoscopy for detection of advanced neoplasia was:

- CTC: 43/46 (sensitivity 100%)
- OC: 46/46 (sensitivity 93.5%)

The sensitivity of the different screening tests for detection of patients with advanced neoplasia is summarized in Figure 9.

**Table 12: Sensitivity and Specificity of Screening Tests For Detection of Patients With Colonic Adenomas**

Test	>9 mm		≥6 mm	
	Sensitivity	Specificity	Sensitivity	Specificity
OC	100 (86.3-100)	98.6 (96.4-99.6)	97.8 (88.5-99.9)	95.8 (92.6-97.9)
CTC	92 (74-99)	97.9 (95.4-99.2)	91.3 (79.2-97.6)	93.1 (89.3-95.9)
FS	68 (46.5-85.1)	99.6 (98-100)	67.4 (52-80.5)	98.9 (96.7-99.8)
FS+FIT	71.4 (47.8-88.7)	85.2 (80.4-89.3)	80 (64.4-90.9)	87.8 (83-91.6)
FS+FOBT	76.2 (52.8-91.8)	89.4 (85-92.9)	70 (53.5-83.4)	89.4 (84.8-93)
FIT	33.3 (14.6-57)	85.6 (80.8-89.6)	40 (24.9-56.7)	88.2 (83.4-91.9)
FOBT	23.8 (8.2-47.2)	89.8 (85.4-93.2)	17.5 (7.3-32.8)	89.8 (85.2-93.4)



**Figure 9: Sensitivity of Screening Tests for Detection of Patients with Advanced Neoplasia**

In regards to radiation exposure, this study used low dose protocol and new dose modulation techniques. The mean radiation dose for CT colonography in the study was 4.5 (0.6) mSv (range 3.5-6.1 mSv). The supine scan contributed a mean of 3.2 mSv and the prone scan to a mean of 1.3 mSv. The authors indicated that with a dose modulation technique, they were able to maintain high image quality even in the pelvis area, a region that is prone to image noise-induced artifacts in CT colonography.

Patients enrolled in this study completed a questionnaire regarding their comfort level before and after CT colonography, as well as after colonoscopy. A total of 256 people returned questionnaire from which, only 114 (44.5%) had received sedation for colonoscopy. Although no difference was found between CT

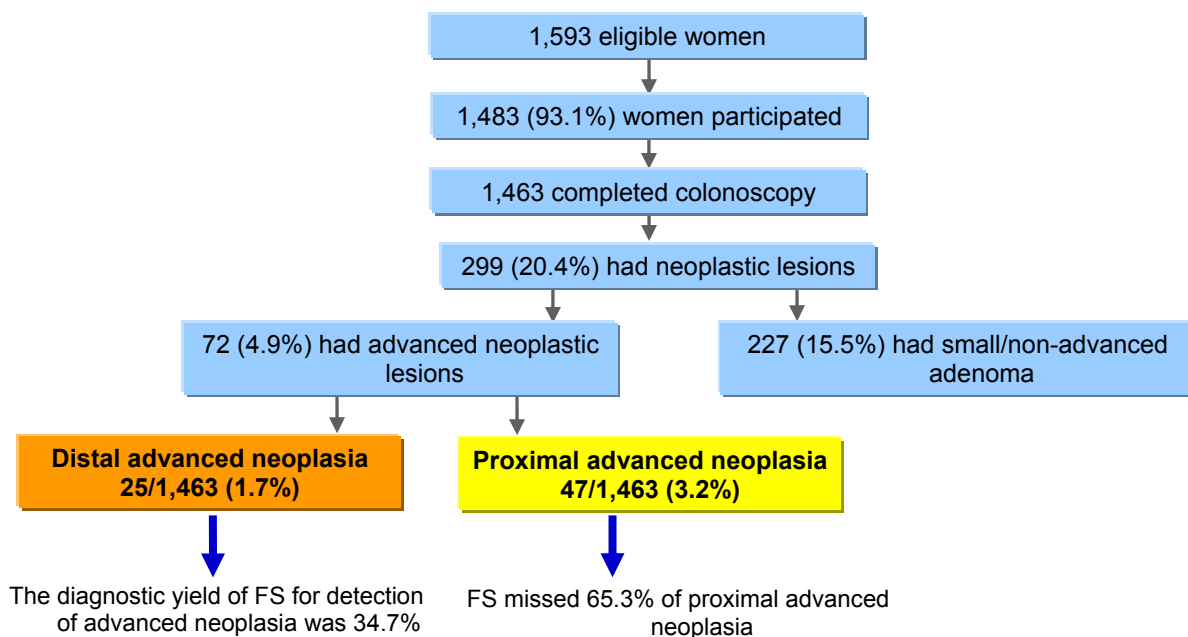
colonography and colonoscopy for those who rated their comfort level as absent, very mild, or mild, the fact that sedation was not used for more than half of the colonoscopic examinations makes it difficult to make any judgment about the patient preference.

Beyond patient comfort levels, the study reported that there was no clinically relevant complication due to OC or CT colonography. Also of note, the reported specificity was based on the detection of adenomas; therefore, it is not an indicator of the proportion of false positive results of CT colonography.

## Studies of High Risk People

### Study on Women Conducted in the United States

Schoenfeld et al. examined the yield of screening colonoscopy in women in the United States to determine whether FS would be a reasonable alternative to colonoscopy in asymptomatic women. (34)The authors also compared the results of colonoscopy in women with the results of a similar study in men (Veterans Affairs Cooperative Study 380). (35) In Schoenfeld’s study, consecutive asymptomatic women referred for CRC screening underwent colonoscopy. The diagnostic yield of FS was calculated by estimating the proportion of people with advanced neoplasia whose lesions would have been identified if they had undergone FS alone. As the detection of small adenomas in the distal colon would trigger the performance of colonoscopy, which would itself detect the advanced neoplasia in the proximal colon, it was reasoned that FS can detect some advanced lesions in the proximal colon. These results showed that advanced colorectal neoplasia would have been detected in 1.7% of the women and missed in 3.2% (see Figure 10). If only FS was performed, its diagnostic yield for advanced neoplasia would have been 34.7% (25/72).



FS indicates flexible sigmoidoscopy. Source:(34)

**Figure 10: Diagnostic Yield of FS for Detection of Advanced Neoplasia in Women**

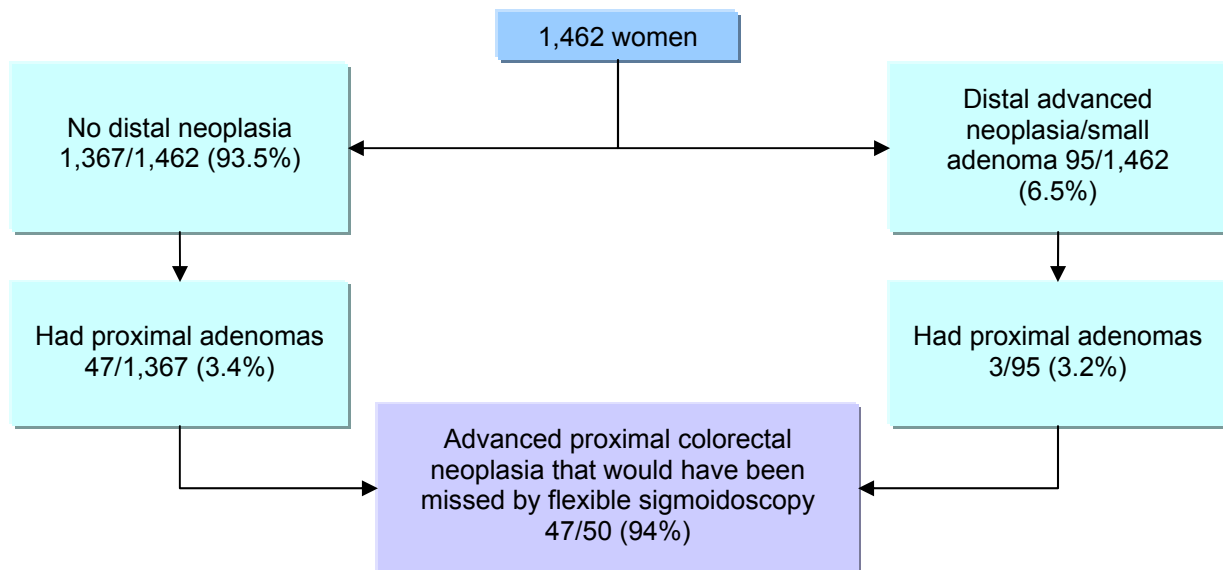
Schoenfeld et al. also found that the proportion of women with advanced neoplasia varied significantly with age (Table 13). Women between the ages of 70 and 79 years exhibited significantly higher rates of advanced neoplasia compared with those between the ages of 50 and 59 [relative risk (RR), 3.56]. When the distal colon was defined as the rectum and sigmoid colon, 95/1462 (6.5%) had advanced colorectal neoplasia or small adenoma in the distal colon that would trigger colonoscopy. It was thus concluded that using FS as screening method in women would result in missing 94% of advanced colorectal neoplasia (see Figure 11).

**Table 13: Proportion of Women With Advanced Neoplasia According to Age**

Age Group	Proportion	Percentage
50–59	26/786	3.3%
60–69	23/420	5.5%
70–79	19/162	11.7%

RR 3.56 (95% CI, 1.70–7.58);  
P = .002 compared with women aged 50–59

CI refers to confidence interval; RR, relative risk. Source: (34)



**Figure 11: Advanced Colorectal Neoplasia Missed by Flexible Sigmoidoscopy**

## Studies on CT Colonography

The CT colonography literature search identified 37 prospective cohort studies (9;36-71) that included a total of 6,868 patients. In each of these studies, colonoscopy was the gold standard for CRC screening and, in most, colonoscopy was performed on the same day as CT colonography (in some it was performed a few days after CT colonography). Overall, CT colonography detected 94% of the cancers. Per-patient sensitivity of CT colonography varied from 48% to 100% for large polyps, 30% to 81% for medium polyps, and 6% to 91% for small polyps. Per-patient specificity for CT colonography was more homogenous across studies at 92% to 100% for large polyps, 80% to 95% for medium polyps, and 86% to 100% for small polyps. A meta-analysis using summary receiver operating characteristic (SROC) methodology was conducted to summarize the results of the studies on performance of CT colonography. The resulting SROC curves for large and medium polyps along with their 95% CI, and related data points are shown in Figures 12 and 13 (page 30).

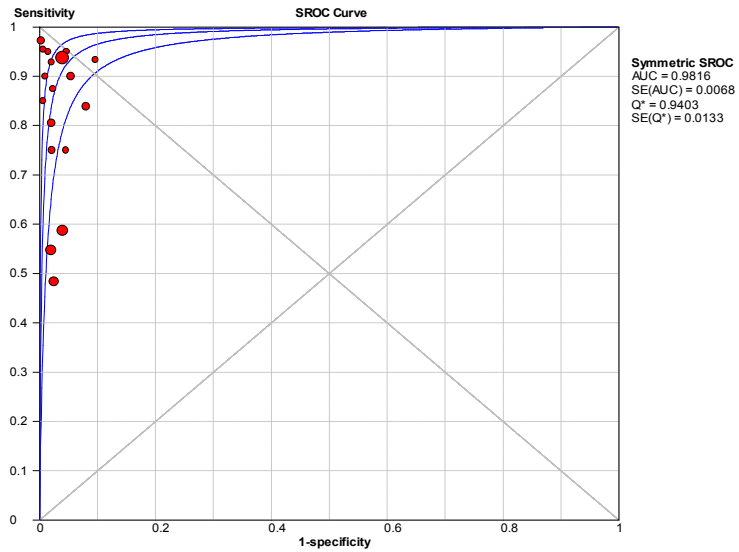
The overall performance level of CT colonography for the identification of large polyps was very high. The SROC curve was located close to the top left corner (indicating high performance), and the AUC was 0.98% [standard error (SE), 0.007]. Studies were heterogeneous in per-patient sensitivity, whereas per-patient specificity was more homogenous across the studies. Forest plots showed that per-patient pooled sensitivity and specificity were 79% and 97%, respectively (see Figures 14–15 on page 30).

It appeared that the higher and homogenous specificity contributed greatly toward a higher value for AUC on the SROC curve. The MAS analysis found that variation in technical parameters was the source of heterogeneity of reported sensitivities. Table 14 shows variation in sensitivity according to different technical parameters.

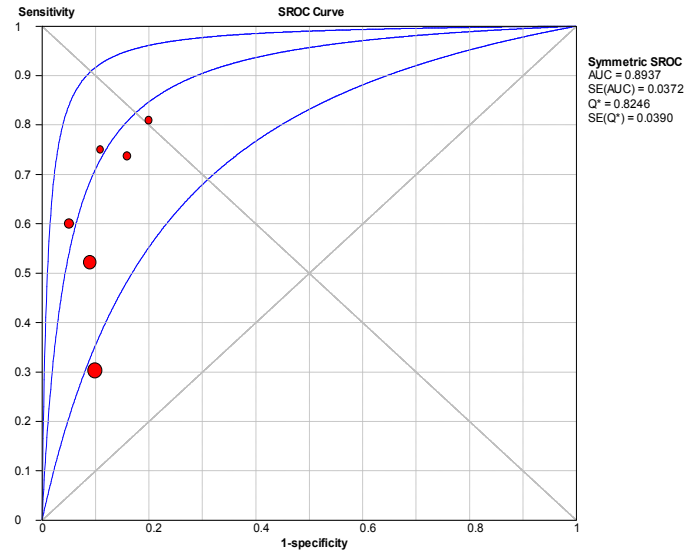
**Table 14: Pooled Sensitivity of CT Colonography for Detection of Colorectal Polyps According to Technical Parameters**

Technical Parameters	Sensitivity (95% CI)		
	Large Polyps	Medium Polyps	Small Polyps
Antegrade/retrograde viewing			
Yes	0.94 (0.88–0.98)	0.83 (0.77–0.88)	0.63 (0.57–0.68)
No	0.76 (0.73–0.79)	0.57 (0.53–0.60)	0.32 (0.30–0.34)
Beam collimation			
≤3 mm	0.83 (0.79–0.86)	0.69 (0.65–0.72)	0.43 (0.41–0.45)
5 mm	0.69 (0.62–0.75)	0.48 (0.42–0.54)	0.16 (0.13–0.18)
Tube current			
≥100 mA	0.90 (0.86–0.93)	0.79 (0.74–0.82)	0.53 (0.49–0.56)
<100 mA	0.72 (0.67–0.76)	0.52 (0.48–0.56)	0.28 (0.26–0.30)
Contrast agents			
Used	0.89 (0.85–0.93)	0.74 (0.68–0.79)	0.40 (0.37–0.44)
Did not use	0.71 (0.67–0.75)	0.59 (0.55–0.62)	0.34 (0.32–0.36)

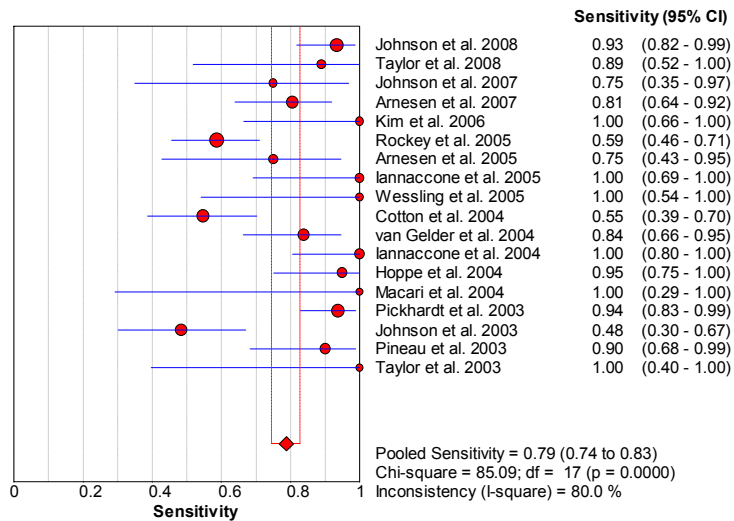
CI refers to confidence interval



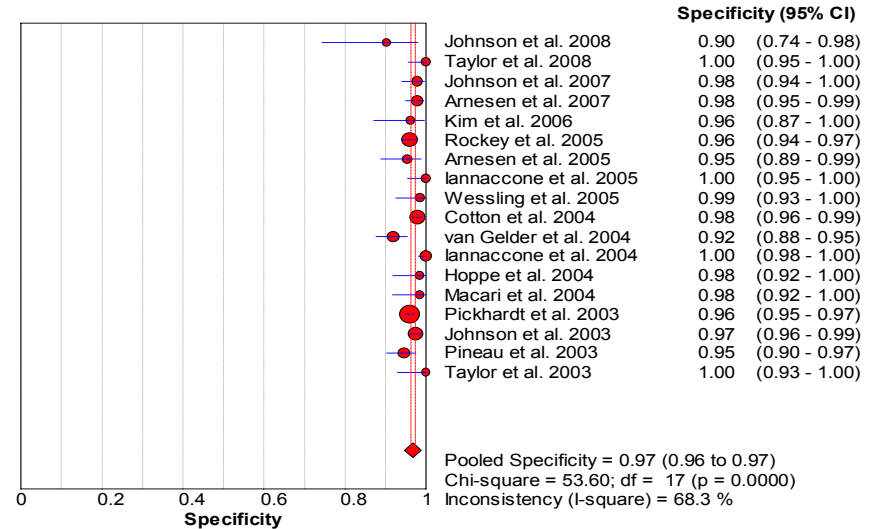
**Figure 12: CT Colonography: SROC Curve for Detecting Patients with Large Polyps**



**Figure 13: CT Colonography: SROC Curve for Detecting Patients with Medium Polyps**



**Figure 14: Sensitivity of CT Colonography for Detecting Patients with Large Polyps**



**Figure 15: Specificity of CT Colonography for Detecting Patients with Large Polyps**

## Studies on MR Colonography

The MR colonography literature search identified 14 prospective cohort studies (72-85) that included a total of 1,305 patients. In each of these studies, the performance of MR colonography was compared with colonoscopy and, in most, optical colonoscopy was performed on the same day as MR colonography.

Overall, 98.2% of cancers were detected by MR colonography. For detection of colorectal polyps, a meta-analysis using SROC methodology was conducted to summarize the results of the studies on per-patient performance of MR colonography. Figures 16 and 17 show the resulting SROC curve for large and medium to large polyps along with 95% CI, and related data points. Per patient sensitivity and specificity of MR colonography for identification of large polyps were 78% and 98% respectively (see Figures 18 and 19 on page 32).

A meta-analysis was conducted to summarize the data on accuracy of MR colonography for polyp detection according to different size category (see Table 15). The specificity of MR colonography and CT colonography for the detection of large ( $\geq 10$  mm) and medium-to-large polyps ( $\geq 6$  mm) are summarized in Table 16. For comparison, the pooled sensitivity of MR colonography and CT colonography for the detection of polyps of different sizes is shown in Figure 20 (page 33).

**Table 15: Pooled Per-Polyp Sensitivity of MR Colonography for the Detection of Colorectal Polyps According to Polyp Size**

Polyp Size	Sensitivity for Polyp Detection, % Mean (Range)		
	Standard/No/Limited BP	Standard BP	Standard BP & Published 2005–2008
Large	82 (74–88)	89 (79–95)	95 (86–99)
Medium	70 (63–76)	81 (73–87)	80 (71–88)
Large & medium	75 (70–79)	85 (79–89)	86 (80–90)
Small	9 (6–13)	8 (5–13)	10 (6–17)

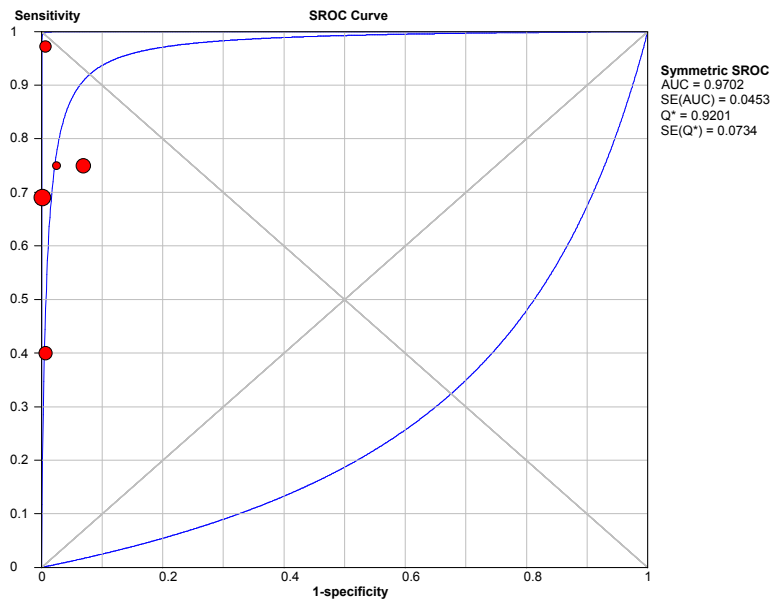
BP indicates bowel preparation.

**Table 16: Specificity of Virtual Colonoscopy Techniques for Detection of Colorectal Polyps**

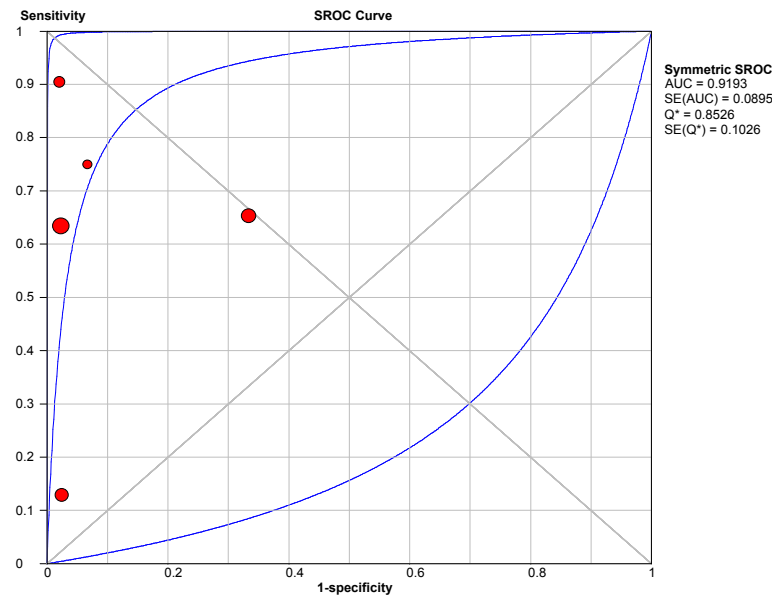
Screening Method	Specificity, (95% CI)	
	Large Polyps	Medium-to-large Polyps
CT colonography	97 (96–97)	84 (83–86)
MR colonography	98 (97–99)	89 (86–91)

CI refers to confidence interval; CT, computed tomography; MR, magnetic resonance.

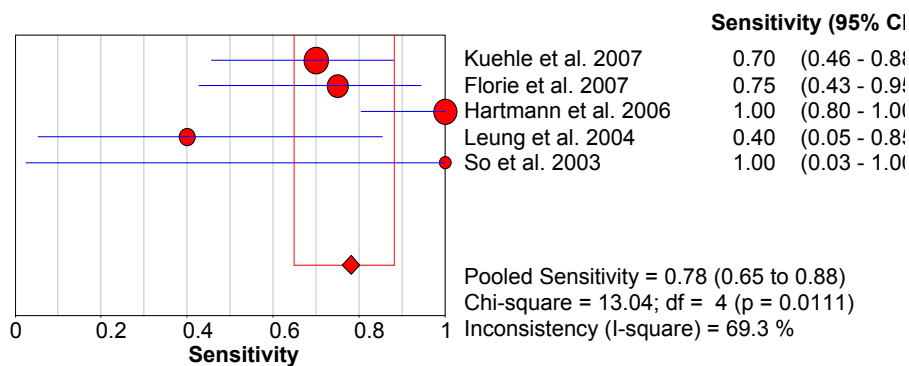




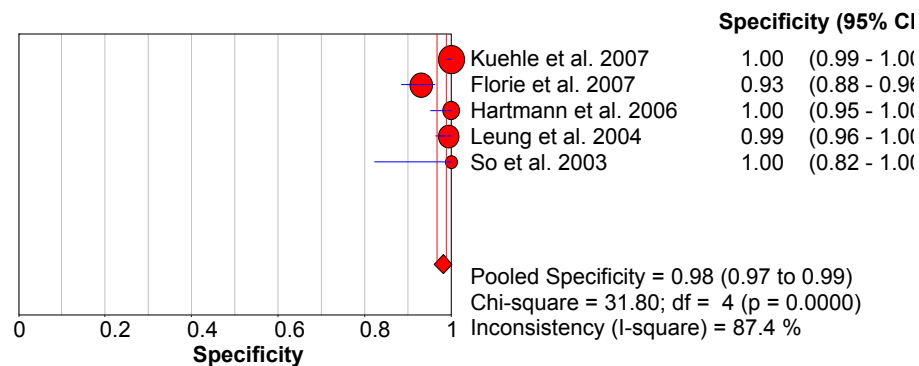
**Figure 16: MR Colonography: SROC Curve for the Detection of Large Polyps**



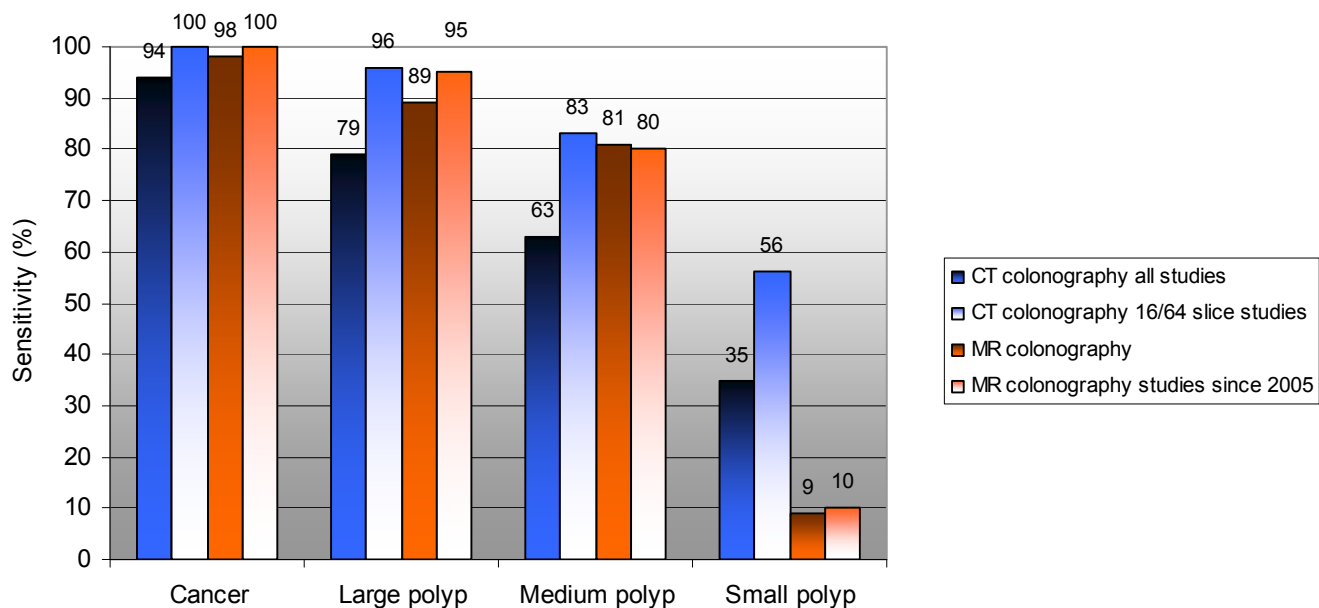
**Figure 17: MR Colonography: SROC Curve for the Detection of Medium-to-Large Polyps**



**Figure 18: Per-Patient Sensitivity of MR Colonography for the Detection of Large Polyps**



**Figure 19: Per-Patient Specificity of MR Colonography for the Detection of Large Polyps**



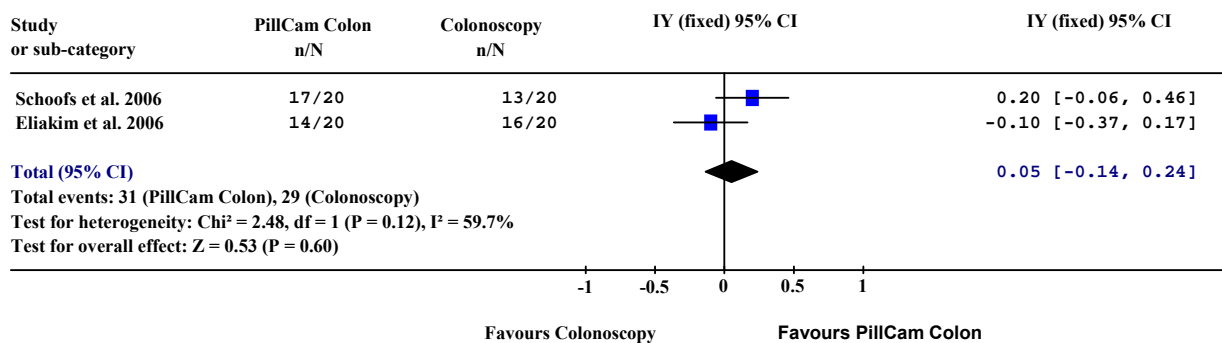
**Figure 20: Pooled Sensitivity of MR Colonography Compared With CT Colonography**

### Studies on Capsule Endoscopy

Two studies (86;87) compared the performance of the PillCam Colon with conventional colonoscopy for the diagnosis of colorectal polyps and cancer. Both studies had limited sample sizes (n=91 and n=41), but were double-blinded in design. Significant findings were defined as a finding of at least one polyp  $\geq 6$  mm in size, or at least three polyps of any size.

A meta-analysis of the diagnostic yield of the PillCam colon and colonoscopy study results was conducted and the incremental yield (IY = yield of PillCam colon minus yield of colonoscopy) and 95% CI calculated using a fixed-effect model. No study heterogeneity was identified across the two studies. The PillCam Colon identified 31 significant polyps while colonoscopy identified 29. The incremental yield (IY) was 0.05 (95% CI, -0.14 to 0.24,  $P = .6$ , see Figure 21).

**Review:** PillCam Colon  
**Comparison:** 01 Yield of Capsule Endoscopy and Colonoscopy  
**Outcome:** 01 For Detection of Polyps  $\geq 6$  mm or  $\geq 3$  Polyps



**Figure 21: Yield of Capsule Endoscopy and Colonoscopy in Detection of Significant Polyps**

## Safety of Colorectal Cancer Screening Methods

### Risk of Colonic Perforation During Endoscopic Techniques

Perforation or haemorrhage during colonoscopy or sigmoidoscopy is mainly occurs in the presence of inflammatory conditions and/or as a consequence of polyp removal. All screening modalities thus carry some risk of perforation in the subsequent therapeutic colonoscopy if a lesion is identified.

A study conducted among the United States Medicare population examined the risk of colonic perforation following colonoscopy and sigmoidoscopy performed for CRC screening and other indications. (88) Overall, 77 perforations occurred after 39,286 colonoscopies (incidence = 1.96/1,000 procedure) and 31 perforations after 35,298 sigmoidoscopies (incidence = 0.88/1,000 procedures). After adjustment, the odds ratio (OR) for perforation from colonoscopy relative to perforation from sigmoidoscopy was 1.8 (95% CI, 1.2–2.8). The risk of perforation in both procedures increased with age ( $P_{\text{trend}} < .001$  for both procedures) and with the presence of two or more comorbidities ( $P_{\text{trend}} < .001$  for colonoscopy and  $P_{\text{trend}} = .03$  for sigmoidoscopy). Subjects aged 75 years and older who underwent colonoscopy exhibited four times the risk of perforation than those aged 65 to 69 years with an OR of 3.7 (95% CI, 1.7–8.2) for those 75 to 79 years and an OR of 3.5 (95% CI, 1.5–7.8) for those 80 years or older. The risk of perforation following sigmoidoscopy among patients 80 years and older was nearly 3 times that observed among those aged 65-69 years [OR, 2.9 (95% CI, 1.1–7.9)].

The risk of perforation following colonoscopy was significantly associated with the presence of two indications: diverticulosis [OR, 2.3 (95% CI, 1.3–4)] and obstruction [OR, 2.9 (95% CI, 1.3–6.7)] compared to those who had screening colonoscopy. In sigmoidoscopy, the risk of perforation was significantly associated with two indications: diverticulosis [OR, 5.4, (95% CI, 2.4–12.4)] and abdominal pain [OR, 2.4, (95% CI, 1.1–5.4)] compared to those who had screening sigmoidoscopy. Neither gender nor race/ethnicity was related to the risk of perforation after a colonoscopy. The incidence of death subsequent to a perforation within 14 days was 51.9/1,000 for colonoscopic perforations and 64.5/1,000 for sigmoidoscopic perforations.

The risk of perforation for those who underwent screening colonoscopy ( $n = 20,163$ ) was 1.3/1,000 and for screening sigmoidoscopy ( $n = 25,951$ ), it was 0.5/1,000. The study also showed that since 1995, the incidence of perforation after colonoscopy in the screening/other group has declined to less than 1 per 1,000.

### Risk of Complications due to Bowel Insufflation during Virtual Colonoscopy Techniques

The advantages of CT colonography and MR colonography techniques compared to colonoscopy are the lower rate of colon perforation and the ability to use scout images to identify the presence of gas following perforation in the peritoneum. Recent data from Sosna et al. (89) and Burling et al. (90) showed perforation rates of 0.05% and 0.06%, respectively, during CT colonography. In the study by Sosna et al. (89), a total of 11,870 CT colonography examinations performed in 11 medical centres between January 2001 and December 2004. There were seven cases of colorectal perforation, yielding a risk ratio of 0.059%. The mean age of patients who had a perforation was 77.8 years. Six of these cases occurred in symptomatic patients at high risk for colorectal neoplasia and one in an asymptomatic average risk individual. Five cases of perforation occurred in the sigmoid colon and one occurred in the rectum. Six cases of perforation occurred in patients in whom a rectal tube was inserted and in five of them, a balloon was inflated. Four patients required surgical treatment. Possible underlying diseases that contributed to perforation were left inguinal hernia containing colon ( $n=3$ ), diverticulosis ( $n=3$ ), and obstructive carcinoma ( $n=1$ ).

In the study by Burling et al. (90), the frequency of serious adverse events associated with CT colonography performed in symptomatic patients were collected through a national survey of 50 centres in UK. From a total of 17,067 CT colonography examinations that were performed, 13 patients (0.08%) had a potentially serious adverse event related to the procedure. Of these, there were three self limiting vasovagal episodes and one episode of cardiac angina. There were nine (0.05%) colonic perforations in which four did not exhibit any perforation symptoms. One patient later required a laparotomy.

## **Risk of Ionizing Radiation Exposure from CT Colonography**

### *Estimation of Risk of Cancer from Exposure to Ionizing Radiation*

Compared with plain-film radiography, CT scanning involves much higher doses of X-ray radiation, resulting in a marked increase in radiation exposure in the population. It has been estimated that 1.5% to 2% of all cancers in the US can be attributed to the radiation from CT scanning. (91) Several recent reports from international organizations have presented cancer risk estimates for exposure to ionizing radiation. The recent report of the committee on Biological Effects of Ionizing Radiation (BEIR VII)<sup>1</sup> provided the most up-to-date and comprehensive risk estimate for exposure to low dose radiation in human subjects. (92) The BEIR VII includes detailed estimates for both cancer incidence and mortality since new and more extensive data have become available since their previous report in 1990.

The BEIR VII report concludes that the current scientific evidence is consistent with the hypothesis that, at the low dose of ionizing radiation such as X-rays and gamma rays, there is a linear dose-response relationship between exposure to ionizing radiation and the development of solid cancers in humans and that there is no threshold. This means that the smallest dose has the potential to cause a small increase in risk of cancer (low dose radiation is defined as doses ranging from nearly zero to 100 mSv). The BEIR VII provided an estimate for the number of cancer cases and deaths expected to arise in 100,000 people exposed to 100 mSv, as well as estimates for cancers of specific sites. The estimated incidence of all solid cancers per 100,000 persons is 800 (400-1600) for males and 1,300 (690-2,500) for females. The estimated incidence of leukemia per 100,000 persons is 100 (30-300) for males and 70 (20-250) for females. About half of the solid cancers and 2/3 of leukemia cases will result in death.

According to the American Cancer Society, the average natural lifetime incidence of cancer in the US is 42 per cent; meaning that 42 out of 100 people will develop some sort of cancer in their lifetime. The BEIR VII lifetime risk model predicts that approximately one individual in 100 people would develop cancer from exposure to radiation with a dose of 100 mSv and approximately one individual in 1,000 would develop cancer from an exposure to 10 mSv. The International Commission on Radiological Protection (ICRP) has estimated the risk of fatal radiogenic cancer caused by CT colonography with a dose of 8 mSv at 0.04%, or 1 in 2,500 individuals. These risk values reported by BEIR and ICRP are comparable as cancer incidence is approximately twice the fatal risk.

Although the risk of developing a radiogenic cancer due to exposure to CT colonography is relatively small (0.04%) in comparison to the natural incidence of cancer (42%), it should be borne in mind that the natural incidence of colon cancer as indicated in BEIR VII is 4,200 per 100,000 people (4.2%) and the fatality from such cancer is about 40 percent (according to the data from Cancer Care Ontario).

Individual risk from exposure to ionizing radiation of CT examination varies significantly depending on factors such as patient age, sex, and expected life span, as well as the absorbed dose. (90) Based on BEIR data, the International Atomic Energy Agency (IAEA) has provided risk estimates of dying from

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<sup>1</sup> The seventh in a series of reports from the National Research Council prepared to advise the US government on the health effects of exposure to ionizing radiation

radiogenic cancers caused by exposure to the radiation during CT colonography at various ages (see Table 17). The risk of dying from such an induced cancer declines as people become older, but it is always higher in females than males.

**Table 17: Potential Lifetime Radiogenic Fatal Cancer Risk for CT colonography at Various Ages**

Gender	Age at Exposure	Fatal Radiogenic Cancer/Leukemia Risk (%)
Male	30	0.030
	40	0.030
	50	0.029
	60	0.026
	70	0.020
	80	0.012
Female	30	0.043
	40	0.041
	50	0.038
	60	0.033
	80	0.015

Reprinted with permission from "Health Risks from Exposure to Low Levels of Ionizing Radiation", 2006 by the National Academy of Sciences, courtesy of the National Academies Press, Washington, D.C., and "Radiation protection in Medical Imaging Techniques: CT Colonography", 2008, courtesy of the International Atomic Energy Agency, Vienna.

The International Commission on Radiological Protection (ICRP) has recommended dose limits for ionizing radiation for those working with radiation and for the public. According to ICRP, the recommended dose limit for occupational exposure is 20 mSv, averaged over 5 years, with the condition that there will be no more than 50 mSv in a single year. For members of the public, the recommended limit is 1mSv per a year. Exceptionally, a higher value of effective dose could be allowed in a year provided that the average over 5 years does not exceed 1 mSv in a year.

## Assessment of Quality of Evidence

Studies that reported mortality as the main outcome were graded using the four elements described in the GRADE approach. Those in which the diagnostic performance of the tests was the main outcome were graded separately using the grade of evidence for diagnostic tests (see Tables 18 to 22). (93)

The quality of the evidence was assessed as being either high, moderate, low, or very low according to GRADE methodology. (94) Accordingly, the following definitions apply:

- High: Further research is very unlikely to change confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Table 23 (page 41) provides an overall summary of the GRADE quality of evidence.

**Table 18: GRADE Quality of Evidence for Fecal Occult Blood Test for Colorectal Cancer Screening: Mortality as End Point of the Studies\***

Outcome	Explanation	GRADE
Design	2 large RCTs	High
Quality	No serious limitations	Unchanged
Consistency	Consistent	Unchanged
Directness	Asymptomatic average-risk people >50 years Age range: Danish and UK study 45–75 years	Unchanged
<b>Quality of evidence</b>		<b>High</b>

\*CRC refers to colorectal cancer, gFOBT, guaiac-based fecal occult blood test; RCT, randomized controlled trial.

**Table 19: GRADE Quality of Evidence for Flexible Sigmoidoscopy, Fecal Occult Blood Test, and Colonoscopy for Colorectal Cancer Screening: Screening Test as a Surrogate for Mortality**

<b>Factor</b>	<b>Explanation</b>	<b>GRADE</b>
<b>Risk of Bias</b>		
Study design	<ul style="list-style-type: none"> <li>One large and one small randomized controlled trial</li> </ul>	High
Limitations	<ul style="list-style-type: none"> <li>No serious limitations</li> </ul>	Unchanged
<b>Indirectness</b>		
Outcomes	<ul style="list-style-type: none"> <li>Diagnostic tests are considered as surrogate outcomes.</li> </ul>	Reduced by one level → Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	<ul style="list-style-type: none"> <li>Study population were average-risk people</li> <li>Level of expertise is not expected to be different from that in Ontario.</li> </ul>	Unchanged
Important inconsistency in study results	<ul style="list-style-type: none"> <li>No inconsistency</li> </ul>	Unchanged
Imprecise evidence	<ul style="list-style-type: none"> <li>There was an adequate number of events.</li> <li>Confidence intervals around the estimate of effect were not large.</li> </ul>	Unchanged
Publication bias	<ul style="list-style-type: none"> <li>No publication bias</li> </ul>	Unchanged
<b>Quality of evidence</b>		<b>Moderate</b>

**Table 20: GRADE Quality of Evidence for CT colonography Method for Colorectal Cancer Screening: Screening Test as a Surrogate for Mortality**

<b>Factor</b>	<b>Explanation</b>	<b>GRADE</b>
<b>Risk of Bias</b>		
Study design	<ul style="list-style-type: none"> <li>▪ I: Australian RCT, multicentre (n=278)</li> <li>▪ II: Johnson et al. 15 centres cohort (n=2,531)</li> <li>▪ III: Graser et al. single centre cohort (n=307)</li> </ul>	High
Limitations	<ul style="list-style-type: none"> <li>▪ Selection of patients or referrals were clearly stated:</li> <li>▪ I &amp; II: Yes</li> <li>▪ III: No</li> <li>▪ New and the gold standard tests were performed in all patients.</li> <li>▪ Evaluators were blinded to the results of the comparative test.</li> </ul>	I & II Unchanged III → Moderate
<b>Indirectness</b>		
Outcomes	<ul style="list-style-type: none"> <li>▪ Diagnostic tests are considered as surrogate outcomes.</li> </ul>	I & II → Moderate III → Low
Patient populations, diagnostic test, comparison test, and indirect comparisons	<ul style="list-style-type: none"> <li>▪ Average risk patients were included in the studies.</li> <li>▪ Tests were directly compared with the reference standard in the same studies but not different studies.</li> </ul>	I & II Unchanged III Unchanged
Important inconsistency in study results	<ul style="list-style-type: none"> <li>▪ No unexplained heterogeneity among studies in reported accuracy</li> </ul>	I & II Unchanged III Unchanged
Imprecise evidence	<ul style="list-style-type: none"> <li>▪ There were an adequate number of events. Confidence intervals around the estimate of effect were not large in most studies.</li> </ul>	I & II Unchanged III Unchanged
Publication bias	<ul style="list-style-type: none"> <li>▪ No publication bias</li> </ul>	I & II Unchanged III Unchanged
<b>Quality of evidence</b>		<b>Moderate</b>



**Table 21: GRADE Quality of Evidence for MR Colonography Method for Colorectal Cancer Screening: Screening Test as a Surrogate for Mortality**

<b>Factor</b>	<b>Explanation</b>	<b>GRADE</b>
<b>Risk of Bias</b>		
Study design	<ul style="list-style-type: none"> <li>▪ Cohort study in which a direct comparison with an appropriate reference standard has been made is considered to be of high quality.</li> </ul>	High
Limitations	<ul style="list-style-type: none"> <li>▪ Studies had no serious limitations.</li> <li>▪ Referral process was clearly stated.</li> <li>▪ New and the gold standard tests were performed in all patients.</li> <li>▪ Evaluators were blinded to the results of the comparative test.</li> </ul>	Unchanged
<b>Indirectness</b>		
Outcomes	<ul style="list-style-type: none"> <li>▪ Diagnostic tests are considered as surrogate outcomes.</li> </ul>	Reduced by one level → Moderate
Patient populations, diagnostic test, comparison test, and indirect comparisons	<ul style="list-style-type: none"> <li>▪ High-risk patients were included in most studies; therefore, the populations included in most studies differ somehow from the average-risk people population.</li> <li>▪ Level of expertise in data interpretation in studies may be higher than that in rural areas of Ontario.</li> <li>▪ Tests were directly compared with the reference standard in the same studies but not different studies.</li> </ul>	Reduced by one level → Low
Important inconsistency in study results	<ul style="list-style-type: none"> <li>▪ No unexplained inconsistency existed. Heterogeneity among studies was found to be due to variation in technical parameters.</li> </ul>	Unchanged
Imprecise evidence	<ul style="list-style-type: none"> <li>▪ There were an adequate number of events. Confidence intervals around the estimate of effect were not large in most studies.</li> </ul>	Unchanged
Publication bias	<ul style="list-style-type: none"> <li>▪ No publication bias</li> </ul>	Unchanged
<b>Quality of evidence</b>		<b>Low</b>

**Table 22: GRADE Quality of Evidence for Capsule Endoscopy Method for Colorectal Cancer Screening: Screening Test as a Surrogate for Mortality**

Factor	Explanation	GRADE
<b>Risk of Bias</b>		
Study design	<ul style="list-style-type: none"> <li>▪ Cohort study in which a direct comparison with an appropriate reference standard has been made is considered to be of high quality.</li> </ul>	High
Limitations	<ul style="list-style-type: none"> <li>▪ Studies had limitations (small sample size).</li> <li>▪ Referral process was clearly stated.</li> <li>▪ New and the gold standard tests were performed in all patients.</li> <li>▪ Evaluators were blinded to the results of the tests.</li> </ul>	Reduced by one level → Moderate
<b>Indirectness</b>		
Outcomes	<ul style="list-style-type: none"> <li>▪ Diagnostic tests are considered as surrogate outcomes.</li> </ul>	Reduced by one level → Low
Patient populations, diagnostic test, comparison test, and indirect comparisons	<ul style="list-style-type: none"> <li>▪ About 40% of the study population was low-risk patients.</li> <li>▪ Level of expertise in data interpretation may be higher than that in rural areas of Ontario.</li> <li>▪ Test was directly compared with the reference standard in the same study but not in different studies.</li> </ul>	Reduced by one level → Very low
Important inconsistency in study results	<ul style="list-style-type: none"> <li>▪ No inconsistency.</li> </ul>	Unchanged
Imprecise evidence	<ul style="list-style-type: none"> <li>▪ There was inadequate number of events. Confidence intervals around the estimate of effect were large in both studies.</li> </ul>	Reduced by one level → Very low
Publication bias	<ul style="list-style-type: none"> <li>▪ No publication bias</li> </ul>	Unchanged
<b>Quality of evidence</b>		<b>Very low</b>

**Table 23: Summary Table for GRADE Quality of Evidence for Methods for Colorectal Cancer Screening**

Screening Method	Studies Reporting on Diagnostic Accuracy of the Test	Studies Reporting on Colorectal Cancer Mortality
CT colonography	Moderate	N/A
MR colonography	Low	N/A
Capsule endoscopy	Very low	N/A
FOBT	Moderate	High
Flexible sigmoidoscopy	Moderate	N/A
Colonoscopy	Moderate	N/A

CRC refers to colorectal cancer; CT, computed tomography; FOBT, fecal occult blood test; MR, magnetic resonance, N/A, not available.

# Economic Analysis

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**Disclaimer:** The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows:

**Hospital:** Ontario Case Costing Initiative cost data are used for all in-hospital stay costs for the designated International Classification of Diseases-10 (ICD-10) diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the secretariat normally defaults to considering direct treatment costs only.

**Nonhospital:** These include physician services costs obtained from the Ontario Schedule of Benefits for physician fees, laboratory fees from the Ontario Laboratory Schedule of Fees, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

**Discounting:** For all cost-effectiveness analyses, a discount rate of 5% is used as per the Canadian Agency for Drugs and Technologies in Health.

**Downstream costs:** All costs reported are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions and are often based on evidence from the medical literature. In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the assumptions, and the revised approach. The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

## Investigation of Existing Canadian Models for Colorectal Cancer

We first explored whether a model existed in Canada that could be adapted to OHTAC's needs. Several collaborations have developed or are currently developing models including:

- Institute for Clinical Evaluative Sciences (ICES)/Cancer Care Ontario (CCO)
- Canadian Agency for Drugs and Technologies in Health (CADTH)/The Province of Alberta
- Statistics Canada

An initial meeting was held with additional discussions thereafter to explore the feasibility and adaptability of these models to the Ontario context. Although they were found to be promising, none could be adapted in time for the September 2008 OHTAC meeting. The decision was, therefore, made to conduct and report on a literature scan and preliminary budget impact analysis of primary screening for CRC.

## Economic Literature Scan of Colorectal Cancer Screening Tools

The inclusion criteria for the economic literature scan were:

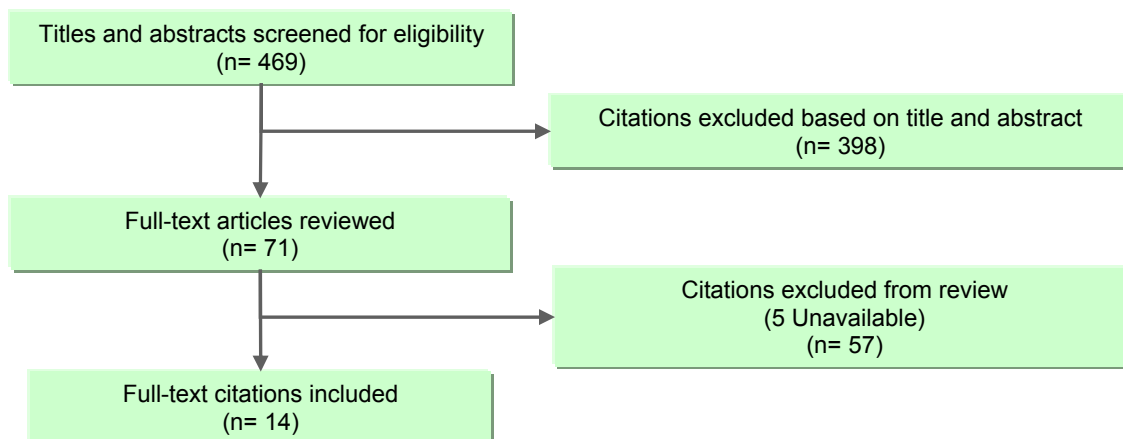
- studies related to screening of CRC (includes colon cancer and rectal cancer)
- studies reporting on the following interventions: virtual colonoscopy (includes CT colonography and MR colonography), capsule endoscopy (CE), fecal occult blood test (FOBT), flexible sigmoidoscopy (FS) and colonoscopy.
- full economic evaluations including cost-effectiveness analyses (CEA), cost-utility analyses (CUA), and cost-benefit analyses (CBA)

Fourteen articles were included in the analysis from the economic literature scan. (95-108) The primary reported outcome was life years gained (LYG) in an average-risk population of persons aged 50 years and older who were eligible for CRC screening. The economic evaluations were Markov models describing the natural course of the disease over an average of a 35-year lifetime. Studies reported incremental cost-effectiveness ratios (ICER) per 100,000 people versus no screening. Outcomes were discounted at 3% to 5%, and sensitivity analyses were conducted in all studies. Figure 22 provides a summary of the literature scan process and the number of abstracts identified, screened, and reviewed for the analysis.

The results of the economic evaluations (Table 24) demonstrated that, although different methods were employed and different results were rendered, overall the screening methods were cost-effective when compared to no screening, while some were dominating. Colonoscopy was generally the most costly procedure and the most effective, preventing the most CRC cases and gaining the most life years.

Notes:

- 1) This review was a preliminary scan of the literature. Individual studies can be reviewed further for details of the methodologies used and the conclusions made.
- 2) All costs are reported in 2008 CAD\$.



**Figure 22: Economic Literature Scan of Colorectal Cancer Screening Tools**

**Table 24: Results of Economic Literature Scan Evaluating Colorectal Cancer Screening Tool versus No Screening**

Screening Method	Frequency	n	CRC Cases Prevented	Life Years Gained	n	ICER Range (CAD\$/LYG)
COL	Every 10 years	8	540 – 4,428	2,130 – 10,669	14	dominates-\$20K
FOBT	Every 1 year	2	380 – 926	1,896 – 2,030	8	dominates-\$40K
FS	Every 3 years	0	-	-	2	\$15K-\$17K
FS	Every 5 years	1	2,027	3,636	5	\$5K-\$39K
FS	Every 10 years	3	390 – 924	1,540 – 3,609	4	dominates-\$14K
CT	Every 10 years	5	785 – 3,705	3,589 – 9,835	5	dominates-\$31K
CE	Every 10 years	1	3,244 – 3,713	8,255 – 8,927	1	\$24K-\$29K

Numbers reported per 100,000 persons for an average lifetime of 35 years

n = number of studies; CAD\$ refers to = Canadian dollars; CE, capsule endoscopy; CRC, colorectal cancer; COL, colonoscopy; CT, computed tomography colonography; FOBT, fecal occult blood test; FS, flexible sigmoidoscopy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; n, number of studies included.

## Cost Impact Analysis of Primary Screening with CRC Screening Tools

A cost impact analysis of primary screening was used to project costs over a 10-year period after positive tests are found with the various screening tools followed by colonoscopy, as directed by established guidelines. (95;109) **Note that only primary screening was tabulated and costed.** Figure 23 describes the series of events that occur after a positive test is confirmed with the various screening tools as per the American Gastroenterological Association (AGA) guidelines. In order to project numbers, population (110) and mortality (111) by age were obtained from Statistics Canada. The eligible population (50 years and older) was screened with:

- FOBT every 2 years to detect CRC cases, or
- CT/MR colonography every 5 years to detect medium-to-large polyps, or
- FS every 5 years to detect medium-to-large polyps, or
- Colonoscopy every 10 years to detect medium-to-large polyps.

Once a positive case is identified with FOBT, a colonoscopy is performed. If the colonoscopy result is positive, the patient then exits the screening program. If the colonoscopy result is negative, the patient then loops back into the program to be screened with FOBT every 2 years. If a positive case is identified with CT/MR colonography, a colonoscopy is also performed. If that result is positive, the patient exits the screening program. If the colonoscopy result is negative, the patient loops back into the program to be screened with CT/MR colonography every 5 years. If a positive case is identified with FS, the patient is followed up with a further colonoscopy. If the result is negative with FS, the patient loops back into the program to be screened with FS every 5 years. If a positive case is identified with colonoscopy, the patient exits the screening program. If the colonoscopy result is negative, the patient loops back into the screening program to be screened with colonoscopy every 10 years.

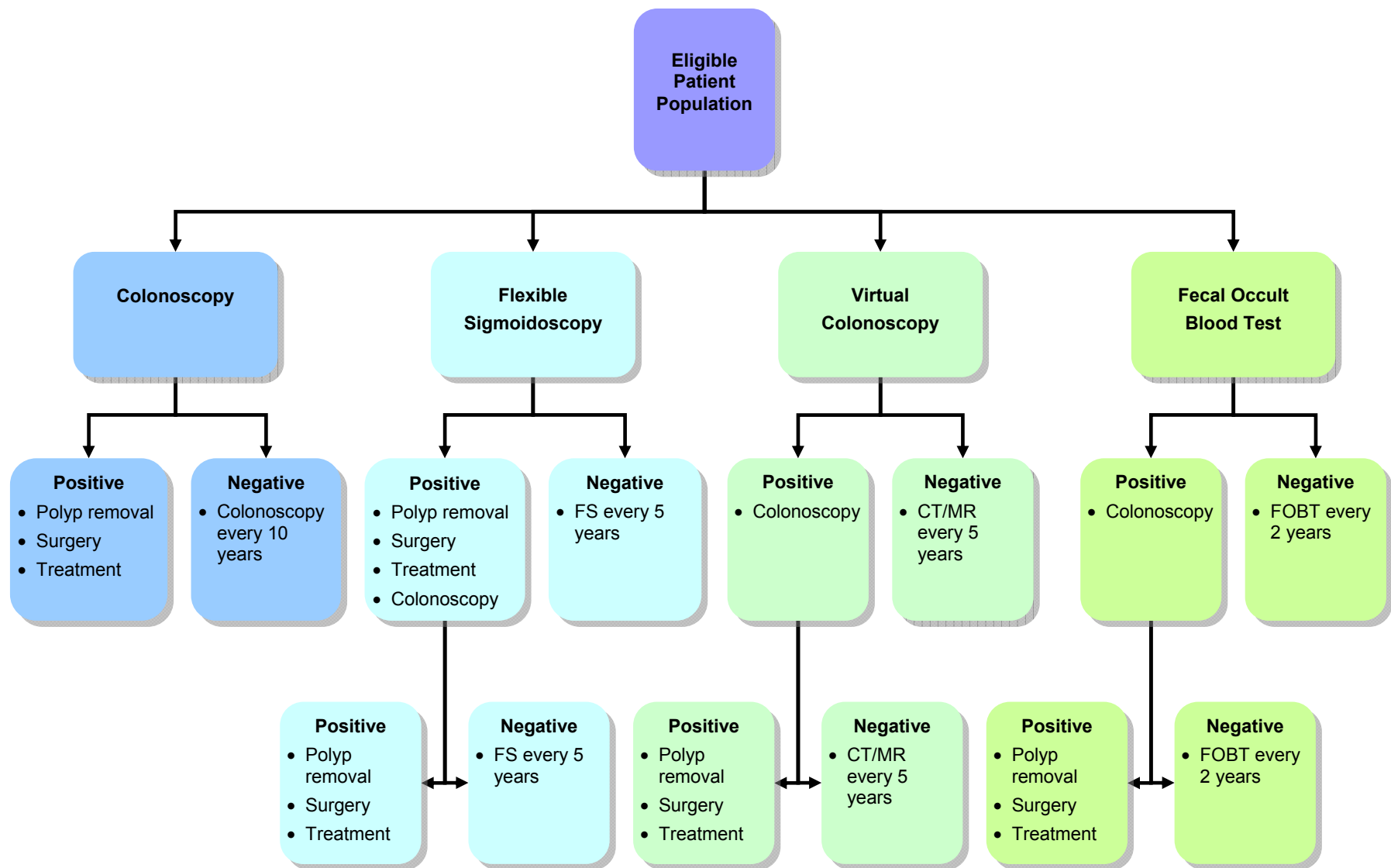


Figure 23: Flow Chart of the Outcomes With the Various Colorectal Cancer Screening Tools

The number of primary screenings was costed over a period of 10 years and total results were reported for all modalities. Flexible sigmoidoscopy may or may not be followed up with a colonoscopy depending on the recommendation. It may also be applied every 3 years instead of 5 years. Recommendations as per AGA guidelines to follow up FS with colonoscopy were used to cost the screening program with FS.

This analysis was limited as downstream costs and events, such as the number of colonoscopies performed with positive cases, surgeries or cancer treatment, were not reported. An economic model would be required to project such outcomes. Furthermore, only primary screening with each modality was costed. Economic models for this disease state are currently under development by various research centres. There may be collaboration among these various stakeholders in the near future and a more accurate prediction of costs may be possible with a refined economic model.

Table 25 describes the positive rates for CRC cases in the case of FOBT and the positive rates for medium to large polyps in the cases of colonoscopy, FS, CT and MR colonography as well as the costs associated with each procedure. Note that colonoscopy was analyzed with two costs: one from the Ontario Case-Costing Initiative (OCCI) and one from CCO. The OCCI cost is based on a weighted average calculation from eight hospitals and includes all direct costs related to the provision of care to the patient. (Personal Communication, Ministry of Health and Long-Term Care, October 2008) The CCO cost is based on a survey administered to participating hospitals and input from the Ontario CRC screening program's clinical advisory committee, made up of experts from across the province and includes all hospital-related expenses for a colonoscopy procedure. (112)

All rates were obtained from published literature. Colonoscopy is considered the gold standard and it was, therefore, assumed that its true positive rate would be 100%. The true positive rates for FS, CT and MR were obtained from the MAS review. Costs were obtained from various sources including the Ministry of Health and Long-Term Care communications, published literature, and websites. The cost of MR colonography was assumed to be the same as that of CT colonography and was obtained from a published Canadian article. (117) The cost of colonoscopy and FS included the cost of the day procedure plus the physician fee associated with the procedure obtained from the Ontario schedule of benefits. Physician fees were not identified for FOBT screening in the average-risk population. For patients with a positive FOBT, however, a physician fee was identified that physicians could claim through the current provincial CRC screening program. This fee was not included in the costing analysis. All costs are reported in 2008 CAD\$.

Table 26 projects the total number of primary screenings with colonoscopy over a 10-year period for screening programs employing different screening tools for CRC. The uptake rate was varied between 25% and 100%. Table 27 projects the total cost of primary screening over a 10-year period for screening programs employing different screening tools for CRC. The uptake rate was again varied between 25% and 100%, and both costs for colonoscopies were used in the analyses.

## **The Ontario Perspective**

In the last Fiscal Year (FY), 411,955 colonoscopies were performed in Ontario in the 50+ population. Tables 28 and 29 (pages 49 and 50) describe the reasons for the use of colonoscopy (the database used was the Provincial Health Planning Database (PHPDB) for FY06/07). For day/night surgeries and emergency procedures, National Ambulatory Care Reporting System (NACRS) data was used. Colonoscopy was identified as the principal intervention and diagnosis was selected as the main problem for the selected population of aged 50+ persons in Ontario. For inpatient cases, the Discharge Abstract Database (DAD) was used. Colonoscopy was identified by CCI code for the selected population of aged 50+ persons in Ontario. Not available (NA) is indicated for those categories with five or fewer visits.

**Table 25: Rates of Positive and Negative Outcomes from the Systematic Reviews of CRC Screening Tools and Cost Per Procedure for Each Screening Modality\*†**

Screening Method	Testing Frequency, Years	Cost, \$	Reference	Positive Rate, %	Negative Rate, %	Reference	True Positive Rate, %	Reference
FOBT	2	50.00	(113)	3	97	Rabeneck (114)	90	Rabeneck (114)
FS	3/5	532.55	(115) ‡	10	90	Giacosa (116)	72	MAS Review
CT Colonography	5	478.53	(117)	30	70	Pickhardt (9)	72	MAS Review
MR Colonography	5	478.53	(117)	30	70	Pickhardt (9)	61	MAS Review
Colonoscopy cost 1	10	519.14	(115)‡	25	75	Giacosa (116)	100	Gold standard
Colonoscopy cost 2	10	457.14	(112;115)	25	75	Giacosa (116)	100	Gold standard

\*CRC refers to colorectal cancer, CT = computed tomography; FOBT = fecal occult blood test; FS = flexible sigmoidoscopy; MR = magnetic resonance.

†FOBT outcome is cancer; for all other screening method the outcome is medium to large polyps.

‡Additional source: Personal Communication, Ontario Ministry of Health and Long-Term Care, October 2008

**Table 26: Total Number of Primary Screenings With Colonoscopy Over a 10-Year Period for Colonoscopy, FS, CT and MR Colonography, and Fecal Occult Blood Test\*†**

Screening Method	Outcome	Number of Screenings			
		100% Uptake	75% Uptake	50% Uptake	25% Uptake
Colonoscopy	Medium to large polyps	5,706,600	4,279,950	2,853,300	1,426,650
FS (every 3 years)	Medium to large polyps	1,576,658	1,182,493	788,329	394,164
FS (every 5 years)	Medium to large polyps	969,896	727,422	484,948	242,474
CT colonography	Medium to large polyps	2,708,440	2,031,330	1,354,220	677,110
MR colonography	Medium to large polyps	2,754,559	2,065,919	1,377,280	688,640
FOBT	Colorectal cancer	639,077	479,307	319,538	159,769

\*CT indicates computed tomography; FS, flexible sigmoidoscopy; MR, magnetic resonance; FOBT refers to fecal occult blood test.

†Total number of primary screenings with colonoscopy over a 10-year period of CRC screening reported.



**Table 27: Total Cost of Primary Screening With OCCI Cost for Colonoscopy Over a 10-Year Period for Colonoscopy, Flexible Sigmoidoscopy, CT and MR Colonography, and Fecal Occult Blood Test\*\*†**

Screening Method	Outcome	Cost, \$ billion			
		100% Uptake	75% Uptake	50% Uptake	25% Uptake
Ontario Case-Costing Initiative costing					
Colonoscopy	Medium to large polyps	3.0	2.2	1.5	0.7
FS (every 3 years)	Medium to large polyps	9.2	6.9	4.6	2.3
FS (every 5 years)	Medium to large polyps	5.7	4.3	2.8	1.4
CT colonography	Medium to large polyps	5.7	4.3	2.9	1.4
MR colonography	Medium to large polyps	5.8	4.4	2.9	1.5
FOBT	Colorectal cancer	1.4	1.0	0.7	0.3
Cancer Care Ontario costing					
Colonoscopy	Medium to large polyps	2.6	2.0	1.3	0.7
FS (every 3 years)	Medium to large polyps	9.1	6.8	4.6	2.3
FS (every 5 years)	Medium to large polyps	5.6	4.2	2.8	1.4
CT colonography	Medium to large polyps	5.6	4.2	2.8	1.4
MR colonography	Medium to large polyps	5.6	4.2	2.8	1.4
FOBT	Colorectal cancer	1.4	1.0	0.7	0.3

\* FS indicates flexible sigmoidoscopy; CT, computed tomography; MR, magnetic resonance; FOBT, fecal occult blood test.

†Total cost of primary screening over a 10-year period of colorectal cancer screening reported.

**Table 28: Reason for Day/Night Surgery, Emergency and Inpatient Colonoscopy Procedures in 50+ Population in Ontario**

<b>Diagnosis Groups (OHIP Billing Code Range)</b>	<b>Outpatient Procedures</b>	<b>Inpatient Procedures</b>	<b>Total Procedures</b>
Certain infectious and parasitic diseases (A00-B99)	85	348	433
Neoplasms (C00-D48)	37,354	2,089	39,443
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	1,992	1,046	3,038
Endocrine, nutritional and metabolic diseases (E00-E90)	80	201	281
Mental and behavioural disorders (F00-F99)	2	96	98
Diseases of the nervous system (G00-G99)	5	58	63
Diseases of the eye and adnexa (H00-H59)	3	1	4
Diseases of the ear and mastoid process (H60-H95)	1	5	6
Diseases of the circulatory system (I00-I99)	6,261	1,132	7,393
Diseases of the respiratory system (J00-J99)	1	447	448
Diseases of the digestive system (K00-K93)	53,763	6,228	59,991
Diseases of the skin and subcutaneous tissue (L00-L99)	70	42	112
Diseases of the musculoskeletal system and connective tissue (M00-M99)	16	103	119
Diseases of the genitourinary system (N00-N99)	87	261	348
Pregnancy, childbirth and the puerperium (O00-O99)	NA	NA	NA
Certain conditions originating in the perinatal period (P00-P96)	NA	1	1
Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	98	8	106
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	5,994	648	6,642
Injury, poisoning and certain other consequences of external causes (S00-T98)	33	288	321
External causes of morbidity and mortality (V01-Y98)	NA	NA	NA
Factors influencing health status and contact with health services (Z00-Z99)	63,445	155	63,600
Provisional Codes for Research and Temporary Assignment (U00-U49) (U50-U99)	NA	NA	NA
<b>Total</b>	<b>169,290</b>	<b>13,157</b>	<b>182,447</b>

Notes: For private practice procedures, the OHIP billing database was searched for FY06/07 with the billing code of E747 (colonoscopy to cecum). Specific diagnoses were identified from the billing schedule and grouped into general categories as identified in the schedule for the selected population of aged 50+ seniors in Ontario. NA is indicated for those categories with 5 or fewer visits.

**Table 29: Reason for Colonoscopy Procedures in Private Practices in the aged 50+ Population in Ontario**

<b>Diagnosis Groups</b>	<b>Total</b>
Accidents, poisoning and violence	25
Complications of pregnancy, childbirth and the puerperium	6
Congenital anomalies	NA
Diseases of blood and blood-forming organs	5,750
Diseases of the circulatory system	3,410
Diseases of the digestive system	137,290
Diseases of the genito-urinary system	135
Diseases of the musculoskeletal system and connective tissue	55
Diseases of the nervous system and sense organs	19
Diseases of the respiratory system	38
Diseases of the skin and subcutaneous system	370
Endocrine, nutritional, metabolic diseases and immunity disorders	89
Infections and parasitic diseases	2,463
Mental disorders	227
Neoplasms	12,341
Perinatal morbidity and mortality	NA
Physiotherapy (OHIP Diagnosis Type 2)	62,921
Supplementary classifications	27
Symptoms, signs and ill-defined conditions	4,336
<b>Total</b>	<b>229,508</b>

It is difficult to comment on how many of these colonoscopies were for CRC screening as there is no specific fee code for screening. According to expert opinion (Personal communication with two clinical experts), however, about 25% of procedures performed in Ontario are for screening. This equates to approximately 103,000 procedures that could have been performed in the last FY for CRC screening in the aged 50+ patient population in Ontario. This figure leads to a total provincial expenditure (with OCCI cost per procedure) of \$53.5M in the last FY for screening colonoscopies.

## Existing Guidelines

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In November 2008, the U.S. Preventive Services Task Force (USPSTF) published an update of its 2002 recommendation statement. (118) It recommended screening for CRC begin at age 50 and continue until age 75 using one of several modalities: high sensitivity FOBT, sigmoidoscopy, and/or colonoscopy. The USPSTF did not recommend routine screening for CRC for adults 75 to 85 years of age and recommended against screening people older than 85 years of age. The USPSTF concluded that for CT colonography and fecal DNA, there is insufficient evidence to permit a recommendation and that the benefit and harms of CT colonography are not yet known.

The relative sensitivity and specificity of the screening modalities used to identify CRC were depicted as:

Sensitivity:

Hemoccult II < immunochemical FOBT ≤ Hemoccult SENS A ≈ flexible sigmoidoscopy < colonoscopy

Specificity:

Hemoccult SENS A < immunochemical FOBT ≈ Hemoccult II < flexible sigmoidoscopy = colonoscopy

According to another recent guideline (109) co-developed by the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology, screening tests for CRC can be grouped into those that primarily detect cancer early and those that both detect cancer early and detect adenomatous polyps, thus providing a greater potential for prevention through polypectomy.

In 2001, the Canadian Task Force on Preventive Health Care (119) published a recommendation for CRC screening. The Task Force concluded that there is good evidence from RCTs to include screening with FOBT in the periodic health examination of asymptomatic people over 50 years of age; however, concerns remain about the high rate of false positive results, feasibility, and small clinical benefit of such screening. It also concluded that the number of patients needed to screen for 10 years to avert one death from CRC is 1,173. Furthermore the Task Force determined that there is fair evidence to include screening with sigmoidoscopy but it is unclear whether one or both of FOBT and FS should be performed.

With regards to colonoscopy, the Task Force reported that there is insufficient evidence to support the use of the technique as a screening method in people of average risk, even though it is the best method for detecting adenomas and carcinomas. Concerns surrounding colonoscopy included poor compliance, the expertise required to perform the procedure, and its potential costs.

# Appendices

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## Appendix 1: Final Search Strategy – Virtual Colonoscopy

Search date: January 30, 2008

Databases Searched: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to January Week 3 2008>

### Search Strategy:

- 1 exp Colonography, Computed Tomographic/ (727)
- 2 (virtual colonoscopy or virtual colonography).mp. (364)
- 3 ((ct or computed tomographic or mr or mri or magnetic resonance) adj2 (colonography or colonoscopy)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (956)
- 4 or/1-3 (1076)
- 5 exp Colorectal Neoplasms/ (51853)
- 6 exp Colonic Polyps/ (2221)
- 7 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (62656)
- 8 exp Precancerous Conditions/ (10419)
- 9 or/5-8 (74178)
- 10 4 and 9 (845)
- 11 limit 10 to (humans and english language and yr="2002 - 2008") (596)
- 12 (meta analy\$ or metaanaly\$ or pooled analysis or random\$ or (systematic\$ adj2 review\$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (376626)
- 13 exp Technology Assessment, Biomedical/ or exp Evidence-Based Medicine/ (30570)
- 14 11 and (12 or 13) (68)
- 15 11 (596)
- 16 limit 15 to (case reports or comment or editorial or letter or "review") (236)
- 17 15 not 16 (360)
- 18 14 or 17 (390)

Database: EMBASE <1980 to 2008 Week 04>

### Search Strategy:

- 1 exp Computed Tomographic Colonography/ (1026)
- 2 (virtual colonoscopy or virtual colonography).mp. (348)
- 3 ((ct or computed tomographic or mr or mri or magnetic resonance) adj2 (colonography or colonoscopy)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1275)
- 4 or/1-3 (1386)
- 5 exp Colorectal Cancer/ (31930)
- 6 exp Colorectal Tumor/ (1892)
- 7 exp Colon Polyp/ (6733)
- 8 exp Colon Adenoma/ (2353)
- 9 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (103335)
- 10 exp "Precancer and Cancer-In-Situ"/ (21099)
- 11 or/5-10 (123356)
- 12 4 and 11 (982)
- 13 limit 12 to (human and english language and yr="2002 - 2008") (688)
- 14 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$) or published studies or published literature or medline or embase or data synthesis or random\$ or data extraction or cochrane).ti.ab. (401281)
- 15 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (277742)
- 16 13 and (14 or 15) (95)
- 17 13 (688)
- 18 limit 17 to (editorial or letter or note or "review") (280)
- 19 Case Report/ (975460)
- 20 17 not (18 or 19) (381)
- 21 16 or 20 (423)

## Appendix 2: Final Search Strategy – Capsule Endoscopy

Search date: October 11, 2007

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to October Week 1 2007>

### Search Strategy:

- 1 exp Capsule Endoscopy/ (178)
- 2 (capsule\$ adj2 (endoscop\$ or Enteroscop\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (785)
- 3 exp Capsule Endoscopes/ (32)
- 4 (pillcam or EndoCapsule or (video adj2 pill) or Sayaka Capsule or (capsule adj2 camera)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (28)
- 5 m2a.mp. (104)
- 6 or/1-5 (858)
- 7 limit 6 to (humans and english language and yr="2003 - 2007") (675)
- 8 (systematic\$ review\$ or meta-analysis or metaanalysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (31364)
- 9 7 and 8 (11)
- 10 7 (675)
- 11 limit 10 to (case reports or comment or editorial or letter or "review") (373)
- 12 10 not 11 (302)
- 13 9 or 12 (308)

Database: EMBASE <1980 to 2007 Week 40>

### Search Strategy:

- 1 exp Capsule Endoscopy/ (842)
- 2 (capsule\$ adj2 (endoscop\$ or Enteroscop\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1146)
- 3 exp Capsule Endoscope/ (114)
- 4 (pillcam or EndoCapsule or (video adj2 pill) or Sayaka Capsule or (capsule adj2 camera)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (37)
- 5 m2a.mp. (129)
- 6 or/1-5 (1232)
- 7 limit 6 to (human and english language and yr="2003 - 2008") (908)
- 8 (systematic\$ review\$ or meta-analysis or metaanalysis).ti,ab. (24452)
- 9 7 and 8 (13)
- 10 7 (908)
- 11 limit 10 to (editorial or letter or note or "review") (368)
- 12 case report.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (966554)
- 13 10 not (11 or 12) (370)
- 14 9 or 13 (380)

## Appendix 3: Final Search Strategy – Sigmoidoscopy Versus Colonoscopy

Search date: November 20, 2007

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, Cochrane Library, and INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to November Week 1 2007>

### Search Strategy:

- 1 exp Colorectal Neoplasms/ (50696)
- 2 exp Colonic Polyps/ (2162)
- 3 ((colon\$ or colorectal) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (54496)
- 4 exp Precancerous Conditions/ (10380)
- 5 or/1-4 (71506)
- 6 exp Colonoscopy/ (7545)
- 7 colonoscop\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (9541)
- 8 6 or 7 (10229)
- 9 5 and 8 (5566)
- 10 exp Sigmoidoscopy/ (1289)
- 11 (proctosigmoidoscop\$ or sigmoidoscop\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2005)
- 12 10 or 11 (2005)
- 13 9 and 12 (1172)
- 14 limit 13 to (humans and english language and yr="2000 - 2007") (824)
- 15 (meta analy\$ or metaanaly\$ or pooled analysis or random\$ or (systematic\$ adj2 review\$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (368180)
- 16 14 and 15 (172)
- 17 14 (824)
- 18 limit 17 to (case reports or comment or editorial or letter or "review") (232)
- 19 17 not 18 (592)
- 20 16 or 19 (627)

Database: EMBASE <1980 to 2007 Week 46>

### Search Strategy:

- 1 exp Colorectal Tumor/ (1870)
- 2 exp Colorectal Cancer/ (31056)
- 3 exp Colon Polyp/ (6647)
- 4 exp COLORECTAL ADENOMA/ (771)
- 5 exp "PRECANCER AND CANCER-IN-SITU"/ (20765)
- 6 ((colon\$ or colorectal) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (92024)
- 7 or/1-6 (111777)
- 8 exp COLONOSCOPY/ (15210)
- 9 colonoscop\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (17394)
- 10 8 or 9 (17394)
- 11 7 and 10 (8716)
- 12 exp SIGMOIDOSCOPY/ (3692)
- 13 (proctosigmoidoscop\$ or sigmoidoscop\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4491)
- 14 12 or 13 (4491)
- 15 11 and 14 (1491)
- 16 limit 15 to (human and english language and yr="2000 - 2007") (881)
- 17 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti.ab. or random\$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (429892)
- 18 16 and 17 (134)
- 19 16 (881)
- 20 limit 19 to (editorial or letter or note or "review") (393)
- 21 Case Report/ (966004)
- 22 19 not (20 or 21) (462)
- 23 18 or 22 (516)

## Appendix 4: Final Search Strategy – FOBT

Search date: February 19, 2008

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, OVID Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1950 to February Week 1 2008>

### Search Strategy:

- 1 exp Colorectal Neoplasms/ (99626)
- 2 exp Intestinal Polyps/ (9490)
- 3 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (115274)
- 4 exp Precancerous Conditions/ (29277)
- 5 or/1-4 (149523)
- 6 exp Occult Blood/ (3280)
- 7 (f?ecal occult blood test\$ or fobt\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1409)
- 8 exp Guaiac/ (201)
- 9 (hemocult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or !nsure or flexsure\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (901)
- 10 or/6-9 (3934)
- 11 5 and 10 (2542)
- 12 limit 11 to (humans and english language and yr="2000 - 2007") (954)
- 13 limit 12 to (controlled clinical trial or meta analysis or randomized controlled trial) (74)
- 14 exp Technology Assessment, Biomedical/ or exp Evidence-based Medicine/ (34553)
- 15 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ab. (67614)
- 16 exp Random Allocation/ or random\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (521780)
- 17 exp Double-Blind Method/ (94539)
- 18 exp Control Groups/ (821)
- 19 exp Placebos/ (26608)
- 20 RCT.mp. (2549)
- 21 or/13-20 (623691)
- 22 12 and 21 (210)

Database: EMBASE <1980 to 2008 Week 07>

### Search Strategy:

- 1 exp Colorectal Cancer/ (32207)
- 2 exp Colorectal Tumor/ (1902)
- 3 exp Intestine Polyp/ (10093)
- 4 exp PRECANCER/ (5925)
- 5 ((colon\$ or colorectal or rectal or rectum) adj5 (precancer\$ or pre-cancer\$ or polyp\$ or neoplasm\$ or adenoma\$ or cancer\$ or dysplasia\$ or neoplasia\$ or tumo?r\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (104003)
- 6 or/1-5 (111136)
- 7 exp Occult Blood Test/ or exp Occult Blood/ (3627)
- 8 (f?ecal occult blood test\$ or fobt\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1328)
- 9 exp GUAIIAC/ (127)
- 10 (hemocult or seracult or coloscreen or Colocare or Guaiac or Ez test or HemeSelect or HemoQuant or !nsure or flexsure\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (733)
- 11 or/7-10 (4071)
- 12 6 and 11 (2596)
- 13 limit 12 to (human and english language and yr="2000 - 2008") (1234)
- 14 Randomized Controlled Trial/ (154426)
- 15 exp Randomization/ (25069)
- 16 exp RANDOM SAMPLE/ (974)
- 17 exp Biomedical Technology Assessment/ or exp Evidence Based Medicine/ (279159)
- 18 (meta analy\$ or metaanaly\$ or pooled analysis or (systematic\$ adj2 review\$) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (56162)
- 19 Double Blind Procedure/ (68240)



20 exp Triple Blind Procedure/ (8)  
21 exp Control Group/ (1423)  
22 exp PLACEBO/ (109985)  
23 (random\$ or RCT).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device  
manufacturer, drug manufacturer name] (400004)  
24 or/14-23 (608529)  
25 13 and 24 (281)

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