Title: Colonoscopy versus Sigmoidoscopy and CT Colonography: A Clinical and Cost Effectiveness Review

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Context and policy issues:

In Canada, colorectal cancer (CRC) remains a leading cause of death, and is the third most common cancer affecting both men and women, with 20,000 cases annually.\(^1\)\(^2\) Many of these cancers are preventable, or can be cured at an earlier stage.\(^1\)\(^3\) Therefore, screening may allow detection of tumours when they are curable, which would result in a better prognosis. This is more clinically meaningful for people at higher risk of CRC, such as those 50 years of age and over, have previous medical history, or have family history.\(^1\)

Commonly used CRC screening strategies include faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), double contrast barium enema, and colonoscopy (COL).\(^4\) In both FS and COL, an endoscope is inserted through the anus into the colon to the cecum in the case of a COL, and only 40cm to 60cm up for an FS.\(^2\) The advantages of COL are its high sensitivity and specificity for the detection of both polyps and carcinomas. Most gastroenterologists agree that COL is the gold standard test. A major disadvantage is that it requires considerable physical resources and skilled personnel; in addition, the complications can result from sedation and the risk of perforation or bleeding are about 1:1000 to 1:2000 cases, so that might affect patient compliance.\(^1\) The advantage of FS is that it is sensitive and specific for distal colonic lesions; however, the disadvantage is that some patients have proximal tumours only, which would not be detected by FS. The risk of perforation is minimal.\(^2\)

Computed tomography colonography (CTC), also known as virtual colonoscopy (VC), is an evolving technique used in CRC screening. It uses data generated from computed tomography to generate 2-dimentional and 3-dimentional images of the colon.\(^5\)\(^6\) It is less invasive, no sedation is needed, has the ability to visualize the whole colon (also the organs outside of colon), and takes less time when compared to FS and COL.\(^7\) On the other hand it is costly, cannot take tissue samples or remove polyps, and therefore it must be followed by colonoscopy if an abnormality is found, which will result in added costs and patient anxiety.\(^7\)
Due to the limited health care resources, and the high cost of cancer screening programs, it is crucial to find an effective but less expensive screening strategy for the target population. The available evidence for the clinical and cost effectiveness of various screening programs will be discussed in the present report. In addition, nurses are trained to undertake some endoscopy examinations, such as sigmoidoscopy. There is a need to assess the clinical- and cost-effectiveness of nurse-directed colonoscopy, as compared to physician-directed colonoscopy.

**Research question:**

1. What is the clinical effectiveness of colonoscopy versus sigmoidoscopy or CT colonography for colorectal cancer screening?

2. What is the cost effectiveness of colonoscopy versus sigmoidoscopy or CT colonography for colorectal cancer screening?

3. Is there any difference in clinical effectiveness or cost effectiveness with nurse-directed versus physician-directed colonoscopy?

**Methods:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/health technology assessments, randomized controlled trials and economic studies.

**Summary of findings:**

No health technology assessments or randomized controlled trials (RCTs) were identified to compare the effectiveness of COL, FS and CTC. No studies were identified that compared the clinical and cost effectiveness between physician-directed colonoscopy and nurse-directed COL.

**Systematic reviews and meta-analyses**

Two meta-analyses were identified. Both studies compared COL with CTC. None of them evaluated the effectiveness of FS. Details of the two studies are summarized in Table 1.

The Rosman review included subjects who underwent CTC and also underwent COL as a reference standard. Some of the included studies attempted to further verify the findings of COL by a second-look COL, or using segmental unblinding during COL, in which the endoscopist was notified of the results of the CTC during withdrawal from each segment of the colon. If a lesion was seen on CTC but not on COL, the segment was then reexamined. The pooled sensitivity of CTC indicated that the accuracy of CTC improved with increasing size of the polyps. Pooled sensitivity of COL was significantly higher than that of CTC when the polyp size was greater than 5mm. The authors suggested that CTC had a reasonable diagnostic accuracy for large polyps but not for smaller polyps.
Walleser et al. examined the clinical and cost effectiveness of CCT compared with COL in symptomatic and high-risk populations (with positive FOBT results or rectal bleeding) in a meta-analysis; an economic evaluation was performed as well.\textsuperscript{10} COL acted as the reference standard and the accuracy of COL was further determined with a second-look COL and/or a clinical follow-up evaluation. For the detection of lesions 10mm or greater, the pooled results from the meta-analysis showed a moderate sensitivity for CTC and a high sensitivity for COL, whereas both tests were highly specific. The differences in sensitivity and specificity between the two tests were statistically significant. For the detection of cancer, the meta-analysis showed high sensitivity and specificity for both tests. Summary estimates of the differences between tests were statistically significant in favour of COL for specificity, but not sensitivity. Results from the economic evaluation are presented later in the current report.

### Table 1: Meta-analyses of CRC Screening Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Population, number of trials</th>
<th>Intervention / Comparator</th>
<th>Results</th>
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<tbody>
<tr>
<td>Rosman et al., 2007\textsuperscript{3}</td>
<td>Subjects underwent CTC (COL as a reference standard) 30 trials</td>
<td>CTC</td>
<td>Pooled per-pt SS for CTC: Polyps 0-5mm: 0.56, 95%CI(0.42-0.70) Polyps 6-10mm: 0.63, 95%CI(0.52-0.75) Polyps &gt;10mm: 0.82, 95%CI(0.76-0.88)</td>
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<tr>
<td></td>
<td></td>
<td>COL was used as gold standard, 9 of the trials verified the findings of COL by using segmental unblinding method during COL, or a second-look COL</td>
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<tr>
<td>Walleser et al., 2007\textsuperscript{10}</td>
<td>FOBT-positive or rectal bleeding pts with lesions ≥10mm or cancer 5 trials</td>
<td>CTC vs. COL Reference standard was COL with a second-look COL and/or clinical follow-up evaluation.</td>
<td>For detection of lesions ≥10mm Pooled SS for CTC: 0.63, 95%CI(0.55-0.71) Pooled SS for COL: 0.95, 95%CI(0.90-0.98), significantly higher than CTC (p=0.04) Pooled SP for CTC: 0.95, 95%CI(0.94-0.97) Pooled SP for COL: 1.00, 95%CI(0.995-1.00), significantly higher than CTC (p&lt;0.001)</td>
</tr>
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</table>

MA – meta-analysis; EE – economic evaluation; CTC – computed tomographic colonography; COL – colonoscopy; pt – patient; SS – sensitivity; SP – specificity; FOBT – fecal occult blood testing
**Economic evaluations**

No economic evaluation was identified comparing the cost effectiveness of physician-directed colonoscopy to nurse-directed colonoscopy.

Eight economic papers were identified.\(^{5,10-16}\) Two of them compared the economic outcomes between COL and FS\(^{11,13}\); four compared COL with CTC\(^{5,10,12,14}\); and two compared COL with CTC and FS.\(^{15,16}\) The trial characteristics of the included economic studies are summarized in Table 2.

Allen et al. conducted a cost-effectiveness analysis comparing watchful waiting, FS, FS + air contrast barium enema and COL, among patients over 40 years of age with asymptomatic rectal bleeding. The incremental cost-effectiveness ratio for COL compared with FS was US$5,480 per quality-adjusted year of life saved (QALY). The cost of COL was reduced to US$1,686 per QALY when age at entry was changed to 45. In all the sensitivity analyses, the incremental cost-effectiveness of COL compared with FS never rose above US$34,000. The authors concluded that COL is a cost-effective method to evaluate otherwise asymptomatic rectal bleeding, with a low cost per QALY compared to other strategies.\(^{11}\)

In the economic study by Ladabaum et al., the cost effectiveness was compared between VC and COL. They found that VC was nearly as clinically effective as COL. However, using a third-party-payer perspective, if test costs were equal, total cost per person was 15% greater for VC than COL, making COL dominated. The authors concluded that even if screening test sensitivities were similar, COL is likely to be preferred over VC unless VC costs significantly less than COL.\(^{12}\)

O’Leary et al. assessed the cost effectiveness of CRC screening programs using a Markov model. They found that in average-risk individuals aged 55-64 years, when compared to no screening, COL was more effective in preventing 35% of CRC, while FS prevented 25% of CRC. FS was more efficient in terms of cost per life-year saved (A$16801), followed by COL (A$19285). They concluded that FS and COL were cost-effective strategies for reducing the disease burden of colorectal cancer.\(^{13}\)

In the only Canadian study by Heitman et al., cost effectiveness of CTC and COL were compared. From the health care purchaser perspective a strategy of CTC for CRC screening would cost C$2.27 million more than COL per 100,000 patients screened; 3.78 perforation-related deaths would be avoided, but 4.11 extra deaths would occur from missed adenomas. Because screening with CTC would cost more and result in more deaths overall compared with COL, the latter remained the dominant strategy. The authors suggested CTC cannot be recommended as a primary means of population-based CRC screening in Canada at present.\(^{14}\)

Hassan et al. studied the cost effectiveness of CTC, COL and FS in the Italian population. They found that COL every 10 years appeared to be the most effective technique preventing 40.9% of CRC, whilst CTC was less effective than COL (38.2%), but more effective than FS (31.8%). However, because COL is more invasive and fewer COLs translate into fewer complications, use of CTC or FS would reduce the complications by 52.6% and 58.1% as compared to those related to COL. When compared to no screening, all the screening programs resulted in cost-savings, allowing a saving of 11€, 17€, and 48€ per person with COL, FS and CTC, respectively. FS appeared to be less cost-effective than CTC, whilst COL appeared to be the most expensive option. Their conclusions were that CTC appeared to be more cost-effective than FS, and it may also become a valid alternative to COL.\(^{15}\)
Pickhardt et al. compared the cost effectiveness of CTC with a 6mm reporting threshold, CTC with no threshold, FS, and COL using a Markov model. Their findings are CTC with a 6mm reporting threshold was the most cost-effective approach at US$4361 per life-year gained. It resulted in a 77.6% reduction in invasive endoscopic procedures.\textsuperscript{16}

Vijan et al. also compared the cost effectiveness of CTC with COL using a Markov model. From a perspective of third-party-payer, the authors found that COL dominates 2-D CTC done every 5 or 10 years. Compared with COL, 3-D CTC done every 5 years is relatively expensive, costing US$156,000 per life-year gained. At 10-year intervals, 3-D CTC is less effective than COL, thus COL is weakly dominant over 3-D CTC. They concluded that CTC is more expensive and generally less effective than COL.\textsuperscript{5}

Finally, in the systematic review conducted by Walleser et al., the authors also performed an economic evaluation. A decision-analytic model was developed to estimate the incremental cost effectiveness of CTC compared with COL in individuals with a positive FOBT. Uncertainty around parameter estimates was explored in one-way and multiway sensitivity analyses. The base case economic analysis showed that CTC is less effective and more costly than COL. At a low prevalence of polyps, sensitivity analysis found CTC was less effective and less costly than COL; the sensitivity analysis also indicated that if CTC was more sensitive than COL, it would be more effective and more costly. Multiway analyses suggest CTC would dominate COL only if it was the more sensitive test and the population tested had a low prevalence of polyps. The authors concluded that CTC appears potentially more costly than COL in individuals with a positive FOBT.\textsuperscript{10}

### Table 2: Economic Evaluations of CRC Screening Tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Patient Population</th>
<th>Comparison</th>
<th>Perspective</th>
<th>Time Horizons</th>
<th>Discount Rate</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Allen et al., 2004\textsuperscript{11}</td>
<td>United States</td>
<td>Pts over age 40 with asymptomatic rectal bleeding</td>
<td>Watchful waiting vs. FS vs. FS+ ACBE vs. COL</td>
<td>Modified societal perspective</td>
<td>lifetime</td>
<td>3%</td>
<td>ICE: ICER for COL compared to FS was $5,480</td>
</tr>
<tr>
<td>Ladabaum et al., 2004\textsuperscript{12}</td>
<td>United States</td>
<td>People aged 50-80ys</td>
<td>VC vs. COL</td>
<td>Third-party-payer</td>
<td>30ys</td>
<td>3%</td>
<td>Incremental cost/LY persons (compared to no screening) COL: $6185 VC: $5563</td>
</tr>
<tr>
<td>O’Leary et al., 2004\textsuperscript{13}</td>
<td>Australia</td>
<td>Average-risk asymptomatic individuals 55-64ys</td>
<td>No screening vs. FS/10y vs. COL/10y vs. FOBT/y vs. FOBT/2y</td>
<td>Government-funded health system</td>
<td>10ys</td>
<td>5%</td>
<td>ICLYS compared with no screening COL: $18,800 VC: $28,700</td>
</tr>
<tr>
<td>Heitman et al., 2005\textsuperscript{14}</td>
<td>Canada</td>
<td>Average-risk pts over the age of 50ys</td>
<td>CTC vs. COL</td>
<td>Health care purchaser</td>
<td>3ys</td>
<td>3%</td>
<td>In a 100,000-pt cohort, CTC would avoid 72,800 COLs, 77 perforations and 3.78 perforation-related deaths; but an additional 3470 small and 1420</td>
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<tr>
<td>Study</td>
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<tr>
<td>Hassan et al., 2007&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Italy</td>
<td>People aged 50-80ys</td>
<td>CTC vs. FS vs. COL</td>
<td>NR</td>
<td>30ys</td>
<td>3%</td>
<td>Compared to no screening, all the screening programs resulted in being cost-saving, allowing a saving of 11€, 17€, and 48€ per person with COL, FS and CTC, respectively.</td>
</tr>
<tr>
<td>Pickhardt et al., 2007&lt;sup&gt;16&lt;/sup&gt;</td>
<td>United States</td>
<td>People aged 50-80ys</td>
<td>No screening vs. CTC vs. FS vs. COL</td>
<td>NR</td>
<td>30ys</td>
<td>3%</td>
<td>Cost per life-year gained CTC (6mm threshold): $4361 CTC (no reporting threshold): $7138 FS: $7404 COL: $9180</td>
</tr>
<tr>
<td>Vijan et al., 2007&lt;sup&gt;5&lt;/sup&gt;</td>
<td>United States</td>
<td>People aged 50-80ys</td>
<td>CTC vs. COL</td>
<td>Third-party-payer, and partly from the societal perspective</td>
<td>10ys</td>
<td>3%</td>
<td>Cost-effectiveness vs. no screening 2-D CTC/5y: $14,290 2-D CTC/10y: $17,280 3-D CTC/5y: $13,460 3-D CTC/10y: $8,150 COL/10y: $8,090</td>
</tr>
<tr>
<td>Walleser et al., 2007&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Australia</td>
<td>Symptomatic and high-risk pts with positive FOBT</td>
<td>CTC vs. COL</td>
<td>Government</td>
<td>lifetime</td>
<td>NR</td>
<td>Base case analysis showed that CTC is less effective and more costly than COL</td>
</tr>
</tbody>
</table>

**Limitations**

- The available evidence from the clinical reviews for the comparison between COL and CTC/FS is very limited. Both included meta-analyses reported merely the accuracy of the tests such as sensitivity and specificity, but not other clinical relevant outcomes (i.e. number of cancers prevented, number of cancer-related deaths prevented, complications resulted from the screening, etc.).
- The accuracy of COL is difficult to evaluate because colonoscopy is commonly used as the reference standard, making the calculation of sensitivity difficult. Few studies attempted to further verify the reliability of COL when it was used as the reference.
- FS was not sufficiently examined in either the clinical reviews or economic reviews. Few studies assessed the effectiveness of FS as compared with CTC. This is probably

Colonoscopy vs. Sigmoidoscopy and CT Colonography

6
because FS is a conventional test in CRC screening; we limited the literature search to include studies published after 2003, so the “older” studies that evaluated FS may have been excluded.

- In the economic evaluations, only one Canadian study was available, to examine the cost-effectiveness of various CRC screening programs from the perspective of Canadian health care purchaser.
- Only English-language publications were considered in this report.
- There were no RCTs or economic evaluations to assess the clinical or cost effectiveness of nurse-directed COL compared to physician-directed COL.

Conclusions and implications for decision or policy making:

In summary, evidence from reviewing clinical effectiveness indicates that COL is effective in screening for CRC with high sensitivity and specificity. CTC has poorer performance in detecting colorectal lesions, especially for smaller size polyps – it may be a reasonable alternative in detecting a large polyp (i.e. greater than 10mm in size), but not when a small polyp may be clinically relevant. No evidence was available to compare the clinical effectiveness of FS with COL.

In the majority of the included economic studies, COL was considered to be more cost-effective than CTC or FS for middle-aged people with high or average-risk of CRC, even though COL-related complications are a concern when deciding on which screening test to use. Most studies indicated that CTC is more expensive and less accurate compared to COL, and suggested that CTC will need to improve its accuracy and reliability, and decrease its cost to be a cost-effective screening option. On the other hand, factors other than the diagnostic accuracy or cost might affect the adoption of a specific test. For example, CTC is dependent on proper bowel preparation. Inadequate bowel preparation and poor bowel distension are reported by most of the authors to be the main reasons for false results. Most of the authors argued that inadequate bowel preparation appears to be a major factor for inaccurate interpretation of data. 17

In the future, more well-designed clinical trials that evaluate the clinically relevant outcomes, more studies that examine the economic outcomes within the Canadian health care system, and studies comparing nurse-directed endoscopy examinations to physician-directed endoscopy examinations, are warranted.

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References:


