APPENDIX 1 (as submitted by author)

Model Design

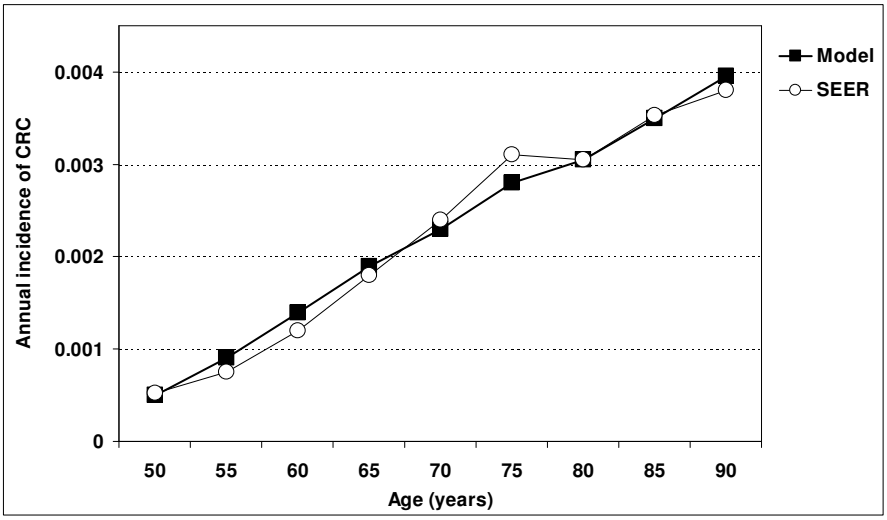
The hypothetical model cohort underwent screening from 50 to 75 years of age. Colorectal cancer is uncommonly diagnosed before 50 years of age at which time the incidence increases in an age-dependent manner. Halting screening at age 75 years is based on the long lead time from normal epithelium to colorectal cancer and that a shorter life expectancy diminishes the benefit of screening. (1) Use of the age range 50 to 75 years is supported by colorectal cancer screening guidelines (2-4) and by decision analyses that have examined commencing and ceasing screening at different ages. (5)

The natural history of colorectal cancer was simulated from normal epithelium to a low risk polyp to an advanced adenoma (size > 9 mm and/or villous histology and/or high grade dysplasia) to cancer. Cancer stages were modeled as localized, regional and distant and could be either pre-clinical (undiagnosed) or diagnosed through investigation of patient symptoms. Superimposed on the natural history of colorectal cancer were ten screening strategies to detect polyps and pre-clinical colorectal cancer. All patients with a polyp detected on the screening test (other than colonoscopy) underwent colonoscopy with polypectomy. If the colonoscopy was negative, then the patient would return to the original screening strategy in the tenth year following the negative colonoscopy. Following polypectomy, these patients underwent a surveillance colonoscopy in five years or in three years if an advanced adenoma was excised. (6) Following a diagnosis of colorectal cancer, patients entered a stage-specific colorectal cancer health state for the next five years during which time they had a yearly probability of dying of other causes, dying of colorectal cancer, or sustaining a relapse. If a patient survived five years without relapse, they were assumed to be disease-free and underwent surveillance colonoscopy every five years. (7)

Model Validation

The annual incidence of colorectal cancer generated by observing a cohort of 100,000 individuals entering the model at age 50 was compared to the Surveillance Epidemiology and End Results data at 5 year intervals from 50 to 100 years. (8) Appendix figure 1 demonstrates that the results from our natural history model were similar to the Surveillance Epidemiology and End Results database.

Appendix Figure 1



Appendix Figure 1. ***Model validation: Colorectal cancer incidence in a cohort of 100,000 individuals.*** **The incidence of CRC in the natural history model is compared to the Surveillance and Epidemiology End Results database.**

Model Assumptions and Limitations

In the natural history model, we assumed all cancers arose from adenomatous polyps. There is emerging data that a small percentage of cancers may arise from flat adenomas rather than polyps. There is some data that fecal occult blood tests and endoscopic examinations have a lower detection rate for flat adenomas as compared to polypoid adenomas. One would expect radiologic studies to also miss these lesions. If this is the case, including flat adenomas in our model would decrease the effectiveness of colorectal cancer screening but likely not change the ranking of the various strategies. We did not allow adenomatous polyps the opportunity to regress as there is little data to support this theory. We assumed that adenoma incidence was unaffected by screening. Both regression of adenomas and decreased adenoma incidence due to screening would decrease the effectiveness of screening. This would have a stronger impact on tests that have a higher sensitivity to adenoma detection.

Sigmoidoscopy was assumed to evaluate the rectum, sigmoid colon and descending colon. Patients did not undergo polypectomy at the time of sigmoidoscopy. Patients with a positive fecal test and negative colonoscopy did not undergo further investigations of occult gastrointestinal bleeding. The model did not incorporate the need for repeat testing with an incomplete examination. No clinical conditions other than polyps or cancer were

incorporated into the model. We assumed that test performance characteristics remained constant on repeat testing.

Markov models do not contain a memory of previous health states such as prior colorectal neoplasia or prior non-compliance with testing. Not modeling an increased higher risk of future adenomas in those with a history of colorectal neoplasia underestimates the decrease in colorectal cancer incidence with screening, particularly for those strategies with a higher sensitivity to detect an advanced adenoma. Compliance was assumed to be random, independent of whether an individual had attended screening in the past. This may not be the case but whether there would be any effect on the model is uncertain.

Transition Probabilities

Natural History of Colorectal Cancer

The prevalence of colorectal neoplasia at age 50 years, the age-specific incidence of low risk polyps, and the annual transition probabilities in the natural history model were derived from colonoscopic screening studies (1, 9-13) and the Surveillance Epidemiology and End Results database. (8) The annual transition probabilities in the natural history model were estimated from the prevalence of low risk polyps, advanced adenomas, pre-clinical cancer and cancer at 50, 60 and 70 years of age. Similarly, the annual probability of diagnosis of a pre-clinical cancer was calculated from the stage distribution of pre-clinical cancer (9-11) to match the stage distribution of cancer from Surveillance Epidemiology and End Results.

Test Performance Characteristics

Test performance characteristics were based on prospective studies using colonoscopy as the gold standard. Per polyp sensitivity and specificity was used for colonoscopy and per patient sensitivity and specificity were used for the other tests as any positive result would lead to a colonoscopy. The mean sensitivities and specificities were calculated for the model input parameters.

For low sensitivity guaiac fecal occult blood test four studies were identified with sensitivities for colorectal cancer detection ranging from 13% to 86%. (14-17) One of these trials used rehydrated specimens and the others unrehydrated. The mean sensitivity (+/-standard deviation used in probabilistic sensitivity analysis) for the detection of cancer was calculated at 46+/-31%. Given the uncertainty around this value, we also performed one-way sensitivity analysis over a range of 13% to 86%.

For high sensitivity guaiac fecal occult blood tests such as Hemoccult II SENSA (16, 18, 19) and fecal immunochemical test (18-23), three and six studies fitting the inclusion criteria were identified, respectively.

For double contrast barium enema, three studies (24-26) meeting the inclusion criteria were identified but only two had data regarding cancer detection. (24, 25)

For colonoscopy and sigmoidoscopy, back-to-back colonoscopy studies and studies comparing colonoscopy to computed tomography (CT) colonography with segmental un-blinding were used. (25, 27-32) Likewise, data from trials comparing CT colonography to colonoscopy with segmental un-blinding determined the performance characteristics of CT colonography used in this study.(25, 29, 31-34)

For fecal deoxyribonucleic acid (DNA) testing, there is one prospective trial of high methodological quality conducted in a screening population (17) in which the DNA integrity assay apparently malfunctioned. (35) Therefore, additional studies using multi-target DNA assay panels in patients with known colorectal adenomas or cancer with or without a comparison to patients with a negative colonoscopy were required to obtain test performance characteristics for fecal DNA. The interval for fecal DNA testing was assumed to be three years based on the expert opinion that the manufacturer's recommended screening interval of five years is too long (3) and the results of an analysis comparing different screening intervals for fecal DNA testing. (36, 37)

Test Complications

The rate of a serious complication with sigmoidoscopy and colonoscopy was taken from a large United States healthcare database. (38, 39) Perforation secondary to CT colonography and double contrast barium enema were also modeled. (40, 41)

Compliance

Individuals may not attend their recommended screening for a variety of reasons some of which may be specific to the screening test. For instance, one study demonstrated that compared to guaiac based fecal occult blood tests, the fecal immunochemical test which does not require as many stool samples or dietary and medication restrictions has improved compliance. (42) Tests requiring a bowel preparation or with a higher complication rate may decrease compliance with screening.

The probabilities of complying with a primary screening test (43-46) and with a colonoscopy following a positive screening test (45-47) were derived from prospective clinical trials studying fecal occult blood tests and sigmoidoscopy in colorectal cancer screening.

Non-compliance was randomly determined at the beginning of each screening cycle. An individual would have the opportunity to resume screening in their next screening cycle independent of past participation. This method of assessing compliance has been used in other models. (48) The mean compliance for initial screening and follow-up colonoscopy were calculated for the model input parameters.

Colorectal cancer outcomes

The stage-specific annual mortality of colorectal cancer was obtained from Surveillance Epidemiology and End Results data (8) for pre-clinical cancer and stage I diagnosed cancer. The stage-specific annual mortality and relapse rate for diagnosed stage II, III and IV colorectal cancer was obtained from recent trials evaluating oxaliplatin-based chemotherapy for stages II, III and IV. (49, 50) The age-specific all-cause mortality rates for the Canadian population were obtained from the Canadian Life Tables. (51)

Health-Related Quality of Life

Individuals without colorectal cancer were assumed to have a utility of 1 or perfect health-related quality of life. Individuals with colorectal cancer had a decrease in quality of life that was stage-dependent. (52)

The utilities were adapted from patients who had previously undergone removal of a colorectal adenoma and were presented with colorectal cancer stage-dependent health states. (52) The mean utility for each stage was calculated assuming that 30% of colorectal cancer was rectal cancer (53) and 25% of individuals with rectal cancer would require a colostomy. (54)

The quality of life decrements from screening or complications incurred during screening were not taken into account because the attenuation of a short term disutility over an individual's lifetime would render this decrement negligible.

Medical Costs

The cost of guaiac-based fecal occult blood tests incorporated the cost of the testing kit (55), laboratory processing and a general practitioner visit taken from the Ontario Health Insurance Plan. The cost of double contrast barium enema, sigmoidoscopy, colonoscopy and CT colonography were derived from the Ontario Health Insurance Plan, Ontario Nurse's Association Collective Agreement and hospital administration data. (56) The costs for sigmoidoscopy and colonoscopy closely approximated the costs obtained from a time-in-motion microcosting study performed at our institution. (57) The cost of the fecal immunochemical test was taken from United States data as it is not yet reimbursed in Canada and fecal DNA testing was also derived from United States data as the test is not currently available in Canada. (37)

The cost of a complication was the direct costs incurred by patients admitted for post-colonoscopy perforation identified through the Calgary Health Region administrative database. (58)

The cost of colorectal cancer was stage-specific and divided into initial treatment (year 1 after diagnosis) (59), well-patient follow-up (year 2-5) (60), relapse (59), and terminal care (last 3 months of life) (59).Well-patient follow-up cost was from the Ontario Health Insurance Plan and Hamilton Health Services following Cancer Care Ontario practice

guidelines. (60) The cost of colorectal cancer management was from a population health microsimulation model to estimate average per patient direct costs for the management of CRC. (59) The model was primarily informed by the Ontario Health Insurance Plan and included the cost of physician visits, diagnostic tests, surgical procedures, radiation therapy, and hospital admissions. Given the recent advances in the adjunctive and palliative treatment of colorectal cancer, the cost of chemotherapy was adjusted from Maroun et al. (59) The chemotherapy regimens modeled for stage II, III, IV and cancer relapse were based on recent clinical trials (49, 61, 62) and supported by the National Comprehensive Cancer Network 2007 guidelines. (63) The cost of these chemotherapy agents and their administration was obtained from the pharmacy department of the British Columbia Cancer Agency.

All costs were inflated to 2007 Canadian dollars using the health component of the consumer price index. (64)

Base Case Analysis

We estimated the incremental cost-effectiveness ratios for each strategy by first rank ordering all strategies according to increasing quality adjusted life years. Strategies with a higher cost and less effective outcome compared with the strategy directly below in the table were considered to be dominated; these were removed from the analysis and incremental cost and quality adjusted life years were calculated between successive strategies that remained. As a last step, strategies exhibiting extended dominance (whose incremental cost effectiveness ratio was higher than a more effective screening strategy) were also removed and final incremental cost effectiveness ratios were calculated between remaining strategies. Although the previously described method for evaluating cost-effectiveness is standard when multiple interventions are being evaluated, we also calculated the incremental cost effectiveness ratio for each pair-wise combination as not all strategies may be feasible in different jurisdictions and individuals may chose a screening strategy based on personal preference. Finally, we calculated the reduction in colorectal cancer mortality and incidence as well as the increase in cost for each screening strategy compared to not screening.

Sensitivity Analysis

Deterministic sensitivity analysis was performed on the variables of test performance, test cost, test compliance and the cost of treating colorectal cancer. The costs were assessed over a broad range to incorporate United States costs for screening tests (37, 65, 66) and chemotherapy. (67) Compliance was further assessed by modeling scenarios in which compliance to all testing was low and in which compliance to fecal testing was low compared to radiologic and endoscopic testing.

To capture variability around point estimates simultaneously, a probabilistic sensitivity analysis was performed. (68) Each parameter in the model was sampled from a statistical distribution by a second order Monte Carlo simulation built into the Markov model. The Monte Carlo simulation randomly selects values from each input parameter's distribution

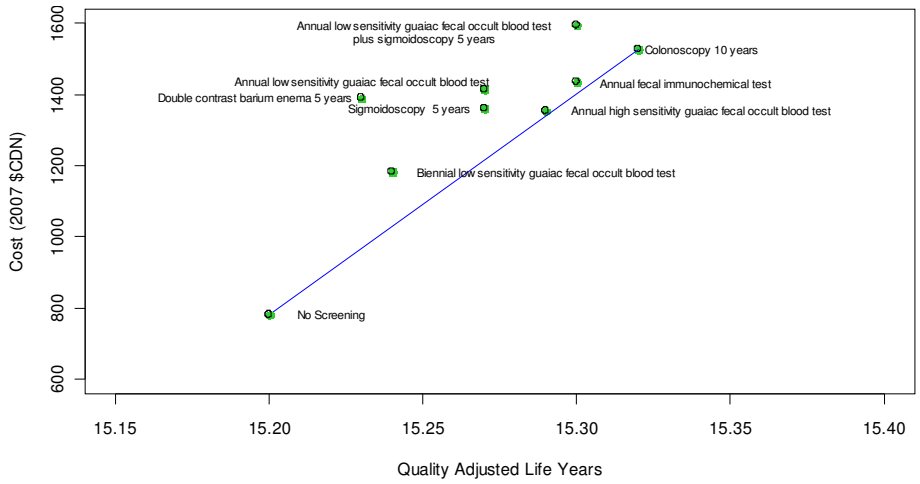
and generates results for that combination of values. This process was repeated 10,000 times. Gamma distributions were fitted to cost parameters, and beta distributions were fitted to utilities and transition probabilities using the input parameter estimates and standard deviations shown in Table 2. The standard deviations were derived from the cited publications or assumed to be ± 30% of the input parameter when insufficient data was available to calculate the standard deviation. The results of the probabilistic sensitivity analysis are presented as incremental cost effectiveness ratios and in a net benefit analysis. A net benefit analysis translates all outcomes into monetary values. (69) We calculated the net benefit statistic for each of the 10,000 simulations based on decision-makers' willingness-to-pay for colorectal cancer screening. A positive net-benefit indicates that the strategy is cost-effective for a given willingness-to-pay and the proportion of these positive net-benefits can be represented graphically through a cost-effectiveness acceptability curve. (70)

Results

Base case analysis

The results from the base-case analysis are shown in Appendix Table 1 and Appendix Figure 2. All ten screening strategies for colorectal cancer increased the quality adjusted life expectancy and were more costly than not screening. Biennial low sensitivity guaiac fecal occult blood test such as Hemoccult II, annual high sensitivity guaiac fecal occult blood test such as Hemoccult II SENSA, annual fecal immunochemical test and colonoscopy every 10 years remained the preferred strategies once the dominated strategies were removed. The incremental cost-effectiveness ratios ranged from $3,660 to $10,025 per quality-adjusted life year gained. When strategies were eliminated through extended dominance, annual high sensitivity guaiac fecal occult blood test and colonoscopy every ten years remained with incremental cost-effectiveness ratios of $6,161 and $6,407 per quality-adjusted life year gained, respectively. The pair-wise incremental cost-effectiveness ratio for each strategy is presented in Appendix Table 2.

Appendix Figure 2



Appendix Figure 2. ***Cost-effectiveness plane for not screening and selected strategies for colorectal cancer screening.*** **The average discounted quality-adjusted life expectancy (years) and cost for the colorectal cancer screening strategies. Those strategies lying above the line are more expensive and less effective than another strategy examined (dominated).**

Appendix Table 3 demonstrates the decreased colorectal cancer incidence and mortality in hypothetical cohorts of 100,000 persons entering each strategy at age 50 years. In a cohort not attending colorectal cancer screening 6257 will be diagnosed with colorectal cancer during their lifetime and 3814 will die of their disease. In the cohorts undergoing colorectal cancer screening there was a decrease in colorectal cancer mortality that ranged from 39% for double contrast barium enema every five years and biennial low sensitivity guaiac fecal occult blood test to 83% for colonoscopy every ten years and a decrease in colorectal cancer incidence ranging from 26% for biennial low sensitivity guaiac fecal occult blood test to 81% for colonoscopy every ten years. Screening yielded from 3198 to 12,013 additional quality-adjusted life years per 100,000 individuals for double contrast barium enema every five years and colonoscopy every ten years, respectively. The cost to screen for colorectal cancer ranged from $40 million to $135 million over the lifetime of 100,000 individuals.

Sensitivity analysis

In general, as the test sensitivity for advanced adenomas rose, the strategy cost decreased and the effectiveness increased (Appendix Table 4). However, increasing test sensitivity for colorectal cancer resulted in a small increase in cost and strategy effectiveness. The

model was influenced by varying the sensitivity of the fecal occult blood tests for advanced adenomas as shown in Appendix Table 5. For instance, if fecal immunochemical test sensitivity for advanced adenomas was less than 30%, then annual fecal immunochemical test was dominated by annual high sensitivity guaiac fecal occult blood test.

When high sensitivity guaiac fecal occult blood test costs more than $13 or sigmoidoscopy costs less than $189, annual high sensitivity guaiac fecal occult blood test no longer dominates sigmoidoscopy every five years. When fecal immunochemical test costs more than $36, annual fecal immunochemical test becomes dominated by colonoscopy every ten years. Computed tomography (CT) colonography every five years remained dominated by one of the other strategies in all scenarios unless the test cost was below $200. Under no circumstances was colonoscopy every ten years dominated by one of the other strategies.

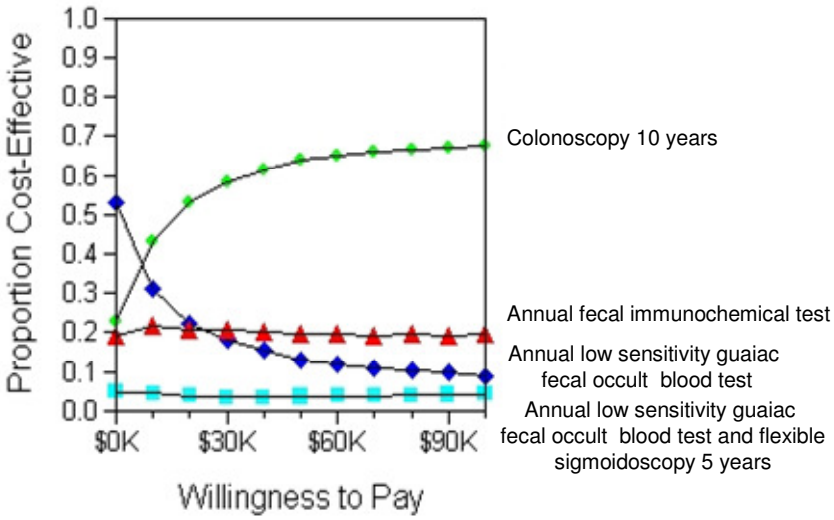
As expected, increasing costs of cancer care increased the cost of each strategy. More informatively, when the cost of treating localized cancer was increased, strategies with a higher sensitivity for detecting an advanced adenoma (CT colonography, sigmoidoscopy and colonoscopy), rose less in cost. This was not seen with varying the cost of treating regional or distant colorectal cancer.

Compliance with the screening tests was analyzed over a broad range and, as anticipated, decreased compliance was associated with a decrease in strategy cost. This pattern was more evident for strategies with a shorter screening interval. Table 6 shows the one-way sensitivity analysis of each screening test while the compliance of the other tests is held constant at 73% (the base-case value derived from the literature). When all tests were assumed to have compliance of 40%, the frequent and relatively more expensive strategy annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy every five years was no longer dominated by colonoscopy every ten years by virtue of its lower cost. We also evaluated the effect of a differential compliance between fecal and non-fecal tests: with fecal tests assumed to have a compliance of 40% and the remaining tests a compliance of 73%, annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy every five years decreased in cost such that it was no longer dominated by colonoscopy every ten years with an incremental cost-effectiveness ratio of $17,740 per quality adjusted life year gained.

The probabilistic sensitivity analysis showed no change in strategy dominance, the ranking of fecal DNA every three years and annual low sensitivity guaiac fecal occult blood test shifted due to changes in these strategies' effectiveness, reflecting the large degree of uncertainty around test performance (Appendix Table 5). When strategies were removed by extended dominance, only colonoscopy every ten years remained with an incremental cost-effectiveness ratio of $7223 per quality-adjusted life year gained. At a willingness to pay of $50,000 per quality-adjusted life year gained, the net health benefits analysis indicates that the likelihood of the strategies tested being cost-effective was 64% for colonoscopy every ten years, 20% for annual fecal immunochemical test, 13% for annual high sensitivity guaiac fecal occult blood test, and 3% for annual low sensitivity

guaiac fecal occult blood test plus sigmoidoscopy every five years (Appendix Figure 3). The remaining strategies contribute less than 1% over a range of willingness to pay up to $100,000 per quality-adjusted life year gained and were not included in the acceptability curve. Over conventional levels of willingness to pay, colonoscopy every ten years was the preferred strategy with the highest net health benefit.

Figure 3



Appendix Figure 3. ***Cost-effectiveness acceptability curve.*** **The probability a strategy is cost-effective (y-axis) compared with the alternative strategies for a range of willingness to pay of up to $100,000 per quality adjusted life year gained (x-axis). For figure clarity, only strategies having a probability > 1% of being cost-effective are represented.**

Appendix Table 1. Results from the base-case analysis

Strategy	Mean cost ($)	Mean quality adjusted life years	Incremental cost ($)	Incremental quality adjusted life years	Incremental cost effectiveness ratio
No screening	783	15.196	--	--	--
Double contrast barium enema 5 years	1,392	15.223	609	0.027	Dominated*
Biennial low sensitivity guaiac fecal occult blood test	1,184	15.242	401	0.046	8,717
Fecal DNA 3 years	2,017	15.254	833	0.012	Dominated
Annual low sensitivity guaiac fecal occult blood test	1,415	15.265	231	0.009	Dominated
CT colonography 5 years	2,135	15.267	720	0.002	Dominated
Sigmoidoscopy 5 years	1,363	15.270	179	0.003	Dominated
Annual high sensitivity guaiac fecal occult blood test	1,356	15.289	172	0.047	3,660
Annual fecal immunochemical test	1,437	15.301	81	0.012	6,750
Annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy 5 years	1,597	15.302	160	0.001	Dominated
Colonoscopy 10 years	1,529	15.316	92	0.014	6,133

Remaining (non-dominated strategies)

Strategy	Mean cost ($)	Mean quality adjusted life years	Incremental cost effectiveness ratio	Interpretation	Final Incremental cost effectiveness ratio
No screening	783	15.196	--	--	--
Biennial low sensitivity guaiac fecal occult blood test	1,184	15.242	8,717	Extended† dominance	Removed
Annual high sensitivity guaiac fecal occult blood test	1,356	15.289	3,660		6,161
Annual fecal immunochemical test	1,437	15.301	6,750	Extended dominance	Removed
Colonoscopy 10 years	1,529	15.316	6,133		6,407

*A strategy exists that is more expensive but less effective. Dominated strategies are removed from the analysis and the incremental cost effectiveness ratios of remaining strategies calculated.

†A strategy exists that is more effective and has a lower incremental cost effectiveness ratio. Extended dominance strategies are removed from the analysis and the incremental cost effectiveness ratios of remaining strategies calculated.

Appendix Table 2. Pair-wise comparisons*

Strategy	No screening	Biennial low sensitivity guaiac fecal occult blood test	Annual high sensitivity guaiac fecal occult blood test	Sigmoidoscopy 5 years	Double contrast barium enema 5 years	Annual low sensitivity guaiac fecal occult blood test	Annual fecal immunochemical	Colonoscopy 10 years	Annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy 5 years	Fecal DNA 3 yeas	CT colonography 5 years
No screening	--	--	--	--	--	--	--	--	--	--	--
Biennial low sensitivity guaiac fecal occult blood test	8,821	--	--	--	--	--	--	--	--	--	--
Annual high sensitivity guaiac fecal occult blood test	6,192	3,661	--	--	--	--	--	--	--	--	--
Sigmoidoscopy 5 years	7,892	6,389	Dominates	--	--	--	--	--	--	--	--
Double contrast barium enema 5 years	19,050	Dominates[†]	Dominates	Dominates	--	--	--	--	--	--	--
Annual low sensitivity guaiac fecal occult blood test	9,133	9,729	Dominates	Dominates	595	--	--	--	--	--	--
Annual fecal immunochemical test	6,237	4,264	6,571	2,366	617	640	--	--	--	--	--
Colonoscopy 10 years	6,209	4,622	4,622	3,559	1,550	2,247	6,023	--	--	--	--
Annual low sensitivity guaiac fecal occult blood test plus	7,679	6,822	6,822	7,198	2,761	4,948	156,806	Dominates	--	--	--

sigmoidoscopy 5 years											
Fecal DNA 3 years	21,521	69,783	Dominates	Dominates	24,635	Dominates	Dominates	Dominates	Dominates	--	--
CT colonography 5 years	19,109	37,531	Dominates	Dominates	19,158	Dominates	Dominates	Dominates	Dominates	8,796	--

*The difference in mean cost between the column and row strategies is divided by the difference in mean effectiveness† The top row strategy is less costly and more effective than the left column strategy to which it is being compared.

Appendix Table 3. Cost and effectiveness of ten colorectal cancer screening strategies over the life-time of 100,000 individuals

Strategy	Cost ($)	Quality adjusted life years gained	Deaths prevented	Decrease in colorectal cancer mortality (%)	Colorectal cancer prevented	Decrease in colorectal cancer incidence (%)
Double contrast barium enema 5 years	60,900,000	3198	1481	39	2687	43
Biennial low sensitivity guaiac fecal occult blood test	40,100,000	4541	1505	39	1626	26
Fecal DNA 3 years	123,400,000	5736	1929	51	1816	29
Annual low sensitivity guaiac fecal occult blood test	63,200,000	6914	2113	55	2748	44
CT colonography 5 years	135,200,000	7076	2158	57	3643	58
Sigmoidoscopy 5 years	58,000,000	7349	2331	61	3910	63
Annual high sensitivity guaiac fecal occult blood test	57,300,000	9259	2527	66	3324	53
Annual fecal immunochemical test	65,400,000	10 491	2834	74	4081	65
Annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy 5 years	81,400,000	10 593	3033	80	4924	73
Colonoscopy 10 years	74,600,000	12 013	3157	83	5082	81

Appendix Table 4. Results of one-way sensitivity analysis

Input parameter	Range	Influence on Model	Threshold Value
Test sensitivity to detect an advanced adenoma			
Low sensitivity guaiac fecal occult blood test	0.1-0.4	Annual low sensitivity guaiac fecal occult blood test not dominated by annual high sensitivity guaiac fecal occult blood test	> 0.31
High sensitivity guaiac fecal occult blood test	0.17-0.5	Annual high sensitivity guaiac fecal occult blood test dominated by annual fecal immunochemical test	<0.24
Fecal immunochemical test	0.27-0.61	Annual fecal immunochemical test dominated by annual high sensitivity guaiac fecal occult blood test	<0.30
Fecal DNA	0.15-0.82	No change	--
Double contrast barium enema	0.75-1	No change	--
CT colonography	0.52-1	No change	--
Colonoscopy and sigmoidoscopy	0.88-1	No change	--
Test sensitivity to detect colorectal cancer			
Low sensitivity guaiac fecal occult blood test	0.13-0.8	No change	--
High sensitivity guaiac fecal occult blood test	0.37-1	No change	--
Fecal immunochemical test	0.71-0.96	No change	--
Fecal DNA	0.52-0.91	No change	--
Double contrast barium enema	0.6-1	No change	--
CT colonography	0.75-1	No change	--
Colonoscopy and sigmoidoscopy	0.5-1	No change	--
Test cost (2007 Canadian dollars)			
Low sensitivity guaiac fecal occult blood test	5-20	No change	--
High sensitivity guaiac fecal occult blood test	5-20	Sigmoidoscopy 5 years not dominated by annual high sensitivity guaiac fecal occult blood test	>13
Fecal immunochemical test	10-40	Annual fecal immunochemical test 1 yr dominated by colonoscopy 10 years	>36
Fecal DNA	150-600	No change	--
Double contrast barium enema	100-400	No change	--
CT colonography	200-2000	CT colonography 5 years not dominated by sigmoidoscopy 5 years	<200
Sigmoidoscopy	100-400	Sigmoidoscopy 5 years not dominated by annual high sensitivity guaiac fecal occult blood test	<189
Colonoscopy	200-2000	No change	--

Test compliance			
Follow-up colonoscopy	0.6-0.9	No change	--
Low sensitivity guaiac fecal occult blood test	0.4-0.8	Annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy 5 years not dominated by colonoscopy 10 years	<0.45
		Annual low sensitivity guaiac fecal occult blood test not dominated by annual high sensitivity guaiac fecal occult blood test	<0.65
High sensitivity guaiac fecal occult blood test	0.4-0.8	Annual high sensitivity guaiac fecal occult blood test dominates biennial low sensitivity guaiac fecal occult blood test	<0.45
		Sigmoidoscopy 5 years not dominated by Annual high sensitivity guaiac fecal occult blood test	<0.50
Fecal immunochemical test	0.4-0.8	No change	--
Fecal DNA	0.4-0.8	No change	--
Double contrast barium enema	0.4-0.8	No change	--
CT colonography	0.4-0.8	No change	--
Sigmoidoscopy	0.4-0.8	Sigmoidoscopy 5 years not dominated by Annual high sensitivity guaiac fecal occult blood test	<0.50
Colonoscopy	0.4-0.8	No change	--
Cost of cancer care in year 1(2007 Canadian dollars)			
Stage I	5,000-30,000	Sigmoidoscopy 5 years is not dominated by Annual high sensitivity guaiac fecal occult blood test	>25,000
Stage II	20,000-50,000	Sigmoidoscopy 5 years is not dominated by Annual high sensitivity guaiac fecal occult blood test	>35,000
Stage III	30,000-100,000	No change	--
Stage IV	50,000-600,000	No change	--

Appendix Table 5. Results from the probabilistic sensitivity analysis

Strategy	Mean cost ($)	Mean quality adjusted life years	Incremental cost ($)	Incremental quality adjusted life years	Incremental cost effectiveness ratio
No screening	797	15.217	--	--	--
Double contrast barium enema 5 years	1,405	15.234	608	0.017	Dominated*
Fecal DNA 3 years	2,084	15.238	679	0.004	Dominated
Biennial low sensitivity guaiac fecal occult blood test	1,181	15.257	384	0.040	9,600
CT colonography 5 years	2,171	15.267	990	0.010	Dominated
Sigmoidoscopy 5 years	1,394	15.269	213	0.002	Dominated
Annual low sensitivity guaiac fecal occult blood test	1,417	15.274	23	0.005	Dominated
Annual high sensitivity guaiac fecal occult blood test	1,359	15.292	178	0.035	5,086
Annual fecal immunochemical test	1,450	15.301	91	0.009	10,111
Annual low sensitivity guaiac fecal occult blood test plus sigmoidoscopy 5 years	1,649	15.304	199	0.003	Dominated
Colonoscopy 10 years	1,541	15.320	91	0.019	4,790

Remaining (non-dominated strategies)

Strategy	Mean cost ($)	Mean quality adjusted life years	Incremental cost effectiveness ratio	Interpretation	Incremental cost effectiveness ratio
No screening	797	15.217	--	--	--
Biennial low sensitivity guaiac fecal occult blood test	1,181	15.257	9,600	Extended† dominance	Removed
Annual high sensitivity guaiac fecal occult blood test	1,359	15.292	5,086	Extended dominance	Removed
Annual fecal immunochemical test	1,450	15.301	10,111	Extended dominance	Removed
Colonoscopy 10 years	1,541	15.320	4,790	--	7,223

*A strategy exists that is more expensive but less effective. Dominated strategies are removed from the analysis and the ICERs of the remaining strategies calculated. †A strategy exists that is more effective and has a lower ICER. Extended dominance strategies are removed from the analysis and the ICERs of remaining strategies calculated.

References

1) **Lin OS, Kozarek RA, Schembre DB, et al.** Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. *JAMA*. 2006;295(20):2357-65.
2) **Leddin D, Hunt R, Champion M, et al.** Canadian Association of Gastroenterology and the Canadian Digestive Health Foundation: Guidelines on colon cancer screening. *Can J Gastroenterol*. 2004;18(2):93-9.
3) **Levin B, Lieberman DA, McFarland B, et al.** Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin*. 2008;58(3):130-60.
4) Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2008;149(9):627-37.
5) **Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van Ballegooijen M, Kuntz KM.** Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008;149(9):659-69.
6) **Winawer SJ, Zauber AG, Fletcher RH, et al.** Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology*. 2006;130(6):1872-85.
7) **Rex DK, Kahi CJ, Levin B, et al.** Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2006;130(6):1865-71.
8) National Cancer Institute, DCCPS, Surveillance Research Program. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Public Use, Nov 2003 Sub (1973-2004). 2004.
9) **Regula J, Rupinski M, Kraszewska E, et al.** Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med*. 2006;355(18):1863-72.
10) **Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G.** Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000;343(3):162-8.
11) **Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF.** Results of screening colonoscopy among persons 40 to 49 years of age. *N Engl J Med*. 2002;346(23):1781-5.
12) **Schoenfeld P, Cash B, Flood A, et al.** Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med*. 2005;352(20):2061-8.

13) **Strul H, Kariv R, Leshno M, et al.** The prevalence rate and anatomic location of colorectal adenoma and cancer detected by colonoscopy in average-risk individuals aged 40-80 years. *Am J Gastroenterol*. 2006;101(2):255-62.
14) **Collins JF, Lieberman DA, Durbin TE, Weiss DG.** Accuracy of screening for fecal occult blood on a single stool sample obtained by digital rectal examination: a comparison with recommended sampling practice. *Ann Intern Med*. 2005;142(2):81-5.
15) **Lieberman DA, Weiss DG.** One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med*. 2001;345(8):555-60.
16) **Greenberg PD, Bertario L, Gnauck R, et al.** A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol*. 2000;95(5):1331-8.
17) **Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME.** Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med*. 2004;351(26):2704-14.
18) **Hoepffner N, Shastri YM, Hanisch E, et al.** Comparative evaluation of a new bedside faecal occult blood test in a prospective multicentre study. *Aliment Pharmacol Ther*. 2006;23(1):145-54.
19) **Wong BC, Wong WM, Cheung KL, et al.** A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther*. 2003;18(9):941-6.
20) **Levi Z, Rozen P, Hazazi R, et al.** A quantitative immunochemical fecal occult blood test for colorectal neoplasia. *Ann Intern Med*. 2007;146(4):244-55.
21) **Yoshinaga M, Motomura S, Takeda H, Yanagisawa Z, Ikeda K.** Evaluation of the sensitivity of an immunochemical fecal occult blood test for colorectal neoplasia. *Am J Gastroenterol*. 1995;90(7):1076-9.
22) **Vilkin A, Rozen P, Levi Z, et al.** Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol*. 2005;100(11):2519-25.
23) **Shastri YM, Loitsch S, Hoepffner N, et al.** Comparison of an established simple office-based immunological FOBT with fecal tumor pyruvate kinase type M2 (M2-PK) for colorectal cancer screening: prospective multicenter study. *Am J Gastroenterol*. 2008;103(6):1496-504.
24) **Irvine EJ, O'Connor J, Frost RA, et al.** Prospective comparison of double contrast barium enema plus flexible sigmoidoscopy v colonoscopy in rectal bleeding: barium enema v colonoscopy in rectal bleeding. *Gut*. 1988;29(9):1188-93.
25) **Rockey DC, Paulson E, Niedzwiecki D, et al.** Analysis of air contrast barium enema, computed tomographic colonography, and colonoscopy: prospective comparison. *Lancet*. 2005;365(9456):305-11.
26) **Winawer SJ, Stewart ET, Zauber AG, et al.** A comparison of colonoscopy and double-contrast barium enema for surveillance after polypectomy. National Polyp Study Work Group. *N Engl J Med*. 2000;342(24):1766-72.

27) **Hixson LJ, Fennerty MB, Sampliner RE, McGee D, Garewal H.** Prospective study of the frequency and size distribution of polyps missed by colonoscopy. *J Natl Cancer Inst*. 1990;82(22):1769-72.
28) **Rex DK, Cutler CS, Lemmel GT, et al.** Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology*. 1997;112(1):24-8.
29) **Cotton PB, Durkalski VL, Pineau BC, et al.** Computed tomographic colonography (virtual colonoscopy): a multicenter comparison with standard colonoscopy for detection of colorectal neoplasia. *JAMA*. 2004;291(14):1713-9.
30) **Matsushita M, Hajiro K, Okazaki K, Takakuwa H, Tominaga M.** Efficacy of total colonoscopy with a transparent cap in comparison with colonoscopy without the cap. *Endoscopy*. 1998;30(5):444-7.
31) **Pickhardt PJ, Choi JR, Hwang I, et al.** Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med*. 2003;349(23):2191-200.
32) **Ginnerup Pedersen B, Christiansen TE, Bjerregaard NC, Ljungmann K, Laurberg S.** Colonoscopy and multidetector-array computed-tomographic colonography: detection rates and feasibility. *Endoscopy*. 2003;35(9):736-42.
33) **Pineau BC, Paskett ED, Chen GJ, et al.** Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology*. 2003;125(2):304-10.
34) **Taylor SA, Halligan S, Saunders BP, et al.** Use of multidetector-row CT colonography for detection of colorectal neoplasia in patients referred via the Department of Health "2-Week-wait" initiative. *Clin Radiol*. 2003;58(11):855-61.
35) **Kahi CJ, Rex DK, Imperiale TF.** Screening, surveillance, and primary prevention for colorectal cancer: a review of the recent literature. *Gastroenterology*. 2008;135(2):380-99.
36) **Song K, Fendrick AM, Ladabaum U.** Fecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis. *Gastroenterology*. 2004;126(5):1270-9.
37) **Parekh M, Fendrick AM, Ladabaum U.** As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. *Aliment Pharmacol Ther*. 2008;27(8):697-712.
38) **Levin TR, Conell C, Shapiro JA, Chazan SG, Nadel MR, Selby JV.** Complications of screening flexible sigmoidoscopy. *Gastroenterology*. 2002;123(6):1786-92.
39) **Levin TR, Zhao W, Conell C, et al.** Complications of colonoscopy in an integrated health care delivery system. *Ann Intern Med*. 2006;145(12):880-6.
40) **de Feiter PW, Soeters PB, Dejong CH.** Rectal perforations after barium enema: a review. *Dis Colon Rectum*. 2006;49(2):261-71.
41) **Sosna J, Blachar A, Amitai M, et al.** Colonic perforation at CT colonography: assessment of risk in a multicenter large cohort. *Radiology*. 2006;239(2):457-63.
42) **Cole SR, Young GP, Esterman A, Cadd B, Morcom J.** A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen*. 2003;10(3):117-22.

43) **Hardcastle JD, Chamberlain JO, Robinson MH, et al.** Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996;348(9040):1472-7.
44) **Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O.** Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996;348(9040):1467-71.
45) **Mandel JS, Bond JH, Church TR, et al.** Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993;328(19):1365-71.
46) **Selby JV, Friedman GD, Quesenberry CP, Jr., Weiss NS.** A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med*. 1992;326(10):653-7.
47) **Jorgensen OD, Kronborg O, Fenger C.** A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. *Gut*. 2002;50(1):29-32.
48) **Frazier AL, Colditz GA, Fuchs CS, Kuntz KM.** Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA*. 2000;284(15):1954-61.
49) **Andre T, Boni C, Mounedji-Boudiaf L, et al.** Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350(23):2343-51.
50) **de Gramont A, Boni C, Navarro M, et al.** Oxaliplatin/5FU/LV in adjuvant colon cancer: updated efficacy results of the MOSAIC trial including survival, with a nedian follow-up of six years. *Journal of Clinical Oncology*. 2007;25(18S):AB4007.
51) Statistics Canada. Life Tables, Canada, Provinces and Territories. 2006. Report No.: 84-537-XIE.
52) **Ness RM, Holmes AM, Klein R, Dittus R.** Utility valuations for outcome states of colorectal cancer. *Am J Gastroenterol*. 1999;94(6):1650-7.
53) Cancer statistics 2005. Vol. 2006: National Cancer Institute of Canada.
54) **Sauer R, Becker H, Hohenberger W, et al.** Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med*. 2004;351(17):1731-40.
55) **Flanagan WM, Le Petit C, Berthelot JM, et al.** Potential impact of population-based colorectal cancer screening in Canada. *Chronic Dis Can*. 2003;24(4):81-8.
56) **McGrath JS, Ponich TP, Gregor JC, et al.** Screening for colorectal cancer: the cost to find an advanced adenoma. *Am J Gastroenterol.* 2002;97(11):2902-7.
57) **Sambrook JC, Chui W, Wang H, et al.** Colonoscopy and flexible sigmoidoscopy: A microcosting study evaluating diagnostic procedural costs in an outpatient endoscopy clinic. *Can J Gastroenterol*. 2006;20(Suppl A):AB167.
58) **Heitman SJ, Manns BJ, Hilsden RJ, Fong A, Dean S, Romagnuolo J.** Cost-effectiveness of computerized tomographic colonography versus colonoscopy for colorectal cancer screening. *CMAJ*. 2005;173(8):877-81.
59) **Maroun J, Ng E, Berthelot JM, et al.** Lifetime costs of colon and rectal cancer management in Canada. *Chronic Dis Can*. 2003;24(4):91-101.
60) **Figueredo A, Rumble RB, Maroun J, et al.** Follow-up of Patients with Curatively Resected Colorectal Cancer
Practice Guidelines Report #2-9. 2004.

61) **Goldberg RM, Sargent DJ, Morton RF, et al.** A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol*. 2004;22(1):23-30.
62) **Kuebler JP, Wieand HS, O'Connell MJ, et al.** Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*. 2007;25(16):2198-204.
63) NCCN Clinical Practice Guidelines. Vol. 2007: National Comprehensive Cancer Network; 2007.
64) Statistics Canada. Consumer price index, health and personal care, by province. 2007.
65) **Ladabaum U, Song K, Fendrick AM.** Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? *Clin Gastroenterol Hepatol*. 2004;2(7):554-63.
66) **Vijan S, Hwang I, Inadomi J, et al.** The cost-effectiveness of CT colonography in screening for colorectal neoplasia. *Am J Gastroenterol*. 2007;102(2):380-90.
67) **Meropol NJ, Schulman KA.** Cost of cancer care: issues and implications. *J Clin Oncol*. 2007;25(2):180-6.
68) **Briggs AH.** Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17(5):479-500.
69) **Stinnett AA, Mullahy J.** Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18(2 Suppl):S68-80.
70) **van Hout BA, Al MJ, Gordon GS, Rutten FF.** Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ*. 1994;3(5):309-19.