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ABSTRACT

Background

Colorectal cancer is a leading cause of mortality and morbidity in Ontario. Most cases of colorectal cancer are preventable through early diagnosis and the removal of precancerous polyps. Colon capsule endoscopy is a non-invasive test for detecting colorectal polyps.

Objectives

The objectives of this analysis were to evaluate the cost-effectiveness and the impact on the Ontario health budget of implementing colon capsule endoscopy for detecting advanced colorectal polyps among adult patients who have been referred for computed tomographic (CT) colonography.

Methods

We performed an original cost-effectiveness analysis to assess the additional cost of CT colonography and colon capsule endoscopy resulting from misdiagnoses. We generated diagnostic accuracy data from a clinical evidence-based analysis (reported separately), and we developed a deterministic Markov model to estimate the additional long-term costs and life-years lost due to false-negative results. We then also performed a budget impact analysis using data from Ontario administrative sources. One-year costs were estimated for CT colonography and colon capsule endoscopy (replacing all CT colonography procedures, and replacing only those CT colonography procedures in patients with an incomplete colonoscopy within the previous year). We conducted this analysis from the payer perspective.

Results

Using the point estimates of diagnostic accuracy from the head-to-head study between colon capsule endoscopy and CT colonography, we found the additional cost of false-positive results for colon capsule endoscopy to be $0.41 per patient, while additional false-negatives for the CT colonography arm generated an added cost of $116 per patient, with 0.0096 life-years lost per patient due to cancer. This results in an additional cost of $26,750 per life-year gained for colon capsule endoscopy compared with CT colonography. The total 1-year cost to replace all CT colonography procedures with colon capsule endoscopy in Ontario is about $2.72 million; replacing only those CT colonography procedures in patients with an incomplete colonoscopy in the previous year would cost about $740,600 in the first year.

Limitations

The difference in accuracy between colon capsule endoscopy and CT colonography was not statistically significant for the detection of advanced adenomas (≥ 10 mm in diameter), according to the head-to-head clinical study from which the diagnostic accuracy was taken. This leads to uncertainty in the economic analysis, with results highly sensitive to changes in diagnostic accuracy.

Conclusions

The cost-effectiveness of colon capsule endoscopy for use in patients referred for CT colonography is $26,750 per life-year, assuming an increased sensitivity of colon capsule endoscopy. Replacement of CT colonography with colon capsule endoscopy is associated with moderate costs to the health care system.

PLAIN LANGUAGE SUMMARY

Colorectal cancer is a leading cause of death in Ontario. Several tools are available to detect growths, called polyps, which can develop into cancer. Early detection of polyps can help prevent the development of colorectal cancer and thereby save lives.

Health Quality Ontario was asked to investigate the appropriate use of a new diagnostic procedure, called colon capsule endoscopy, and its economic impact on the health care system. In this procedure, the patient swallows a pill equipped with a tiny camera that takes images of the colon as it passes through the gastrointestinal tract. The images are transmitted to a data recorder that a specialist reviews. The procedure does not require sedation and is less invasive than other procedures used to detect colorectal polyps.

A companion report by Health Quality Ontario looked at the evidence of colon capsule endoscopy for use in patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer. The report found that colon capsule endoscopy has good accuracy in detecting colorectal polyps in adults with higher risk of colorectal cancer. The report also compared the accuracy of colon capsule endoscopy with computed tomographic (CT) scan of the colon (colonography), another diagnostic technique used to detect colorectal polyps, and found no difference in accuracy between the two techniques.

We reviewed existing health economics research and found that the use of capsule endoscopy is costly and that it is preferred for use with average-risk patients *only under certain conditions*. The studies found were not relevant to the Canadian context and looked at capsule endoscopy only as a tool in colorectal cancer screening instead of as an alternative to CT colonography; experts have suggested that the better use of capsule endoscopy would be as an alternative to CT colonography.

Our economic analysis considered the cost of the capsule, direct costs of the procedure, initial consultation with a physician, and the interpretation of the data captured by the capsule after it has passed through a patient. We found that capsule endoscopy is associated with moderate costs to Ontario's health care system. The cost-effectiveness of capsule endoscopy compared with CT colonography is uncertain because it is based on a study that showed the accuracies of the two procedures are not significantly different from each other. Although we calculated an estimate of $26,750 for each year of life gained with the use of capsule endoscopy versus CT colonography, this result can change greatly depending on the diagnostic sensitivity of either test. Consequently, our results are uncertain.

We estimated that the current use of CT colonography costs Ontario about $5.4 million a year. Ontario would have to spend an additional $2.7 million to introduce capsule endoscopy as a replacement for all patients referred for CT colonography. If the colon capsule procedure were to replace CT colonography in only patients who had an incomplete colonoscopy in the previous year, the incremental 1-year cost would be about $740,600. These estimates are for upfront diagnostic costs for 1 year only, and do not include likely changes in costs or potential savings over the longer term.

TABLE OF CONTENTS

LIST OF TABLES **8**
LIST OF FIGURES **8**
LIST OF ABBREVIATIONS **9**
BACKGROUND **10**
Objectives of Analysis 10
Clinical Need and Target Population 11
Description of Disease/Condition *11*
Prevalence and Incidence *11*
Ontario Context *11*
Interventions Under Evaluation 12
Implications in Colorectal Cancer Screening *12*
Research Question 13
ECONOMIC LITERATURE REVIEW **14**
Research Methods 14
Literature Search *14*
Inclusion Criteria *14*
Exclusion Criteria *14*
Results of Economic Literature Review 14
PRIMARY ECONOMIC ANALYSIS **17**
Cost-Effectiveness Model 17
Interventions Evaluated *17*
Target Population *17*
Perspective *18*
Discounting and Time Horizon *18*
Variability and Uncertainty *18*
Model Structure *18*
Model Input Parameters 20
Clinical Model Input Parameters *20*
Natural History Model Input Parameters *20*
Validation 22
Prevalence *22*
Resources and Cost Model Input Parameters *23*
Cost-Effectiveness Analysis Results: Base Case Analysis 25
False-Positive Results *25*
False-Negative Results *25*
Sensitivity Analysis 26
Sensitivity of Colon Capsule Endoscopy and of Computed Tomographic Colonography *26*
Specificity of Computed Tomographic Colonography *26*
Price of Capsule Unit *27*
Proportion of Capsule Retentions Resolved Surgically *27*
Proportion of Patients Treated With Chemotherapy *27*
Prevalence of Advanced Adenomas *27*

BUDGET IMPACT ANALYSIS 29
Research Methods 29
Type of Analysis 29
Perspective 29
Model Input Parameters 29
Resource Utilization 29
Sensitivity Analysis 30
Results of Budget Impact Analysis 30
Colon Capsule Endoscopy as Replacement for All Computed Tomographic Colonography Procedures 30
Colon Capsule Endoscopy as Replacement for Computed Tomographic Colonography in Patients With Prior Incomplete Colonoscopies 31
Sensitivity Analyses 31
LIMITATIONS 33
CONCLUSIONS 34
ACKNOWLEDGEMENTS 35
APPENDICES 36
Appendix 1: Literature Search Strategies 36
Appendix 2: Additional Costing 38
REFERENCES 39

LIST OF TABLES

Table 1: Number of Computed Tomographic Colonographies by Patient Age, in Ontario, 2012 18
Table 2: Natural History Model Inputs 21
Table 3: Validation of Natural History Model 22
Table 4: Complication Rates Used in Model 23
Table 5: Costs of Colon Capsule Endoscopy and Computed Tomographic Colonography, Including Costs for Complications 24
Table 6: Sensitivity and Specificity of Colon Capsule Endoscopy and Computed Tomographic Colonography 25
Table 7: Economic Model Base Case—False-Positive Results 25
Table 8: Economic Model Base Case—False-Negative Results 26
Table 9: Economic Model Base Case—Overall Results 26
Table 10: Sensitivity Analysis—Cost-Effectiveness Model 28
Table 11: Annual Number of Procedures for Computed Tomographic Colonography and Colon Capsule Endoscopy 30
Table 12: Results of Budget Impact Analysis for Colon Capsule Endoscopy Replacing All Computed Tomographic Colonography Procedures 31
Table 13: Results of Budget Impact Analysis for Colon Capsule Endoscopy Replacing Computed Tomographic Colonography in Patients With Prior Incomplete Colonoscopy 31
Table 14: Results of One-Way Sensitivity Analyses—Colon Capsule Endoscopy Replacing All Computed Tomographic Colonography Procedures 32
Table 15: Results of One-Way Sensitivity Analyses—CCE Replacing All CTC Procedures in Patients With Prior Incomplete Colonoscopy 32
Table A1: Additional Costing for Colonoscopy and Double-Balloon Enteroscopy 38

LIST OF FIGURES

Figure 1: Decision Tree for Patients Referred for Computed Tomographic Colonography 19
Figure 2: Long-Term Markov Model 20

LIST OF ABBREVIATIONS

CT	Computed tomographic
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
LYG	Life-year gained
OCCI	Ontario Case Costing Initiative
OHIP	Ontario Health Insurance Plan
QALY	Quality-adjusted life-year

BACKGROUND

The Programs for the Assessment of Technology in Health (PATH) Research Institute was commissioned by Health Quality Ontario to evaluate the cost-effectiveness and predict the short-term costs and effects of colon capsule endoscopy for detection of colorectal polyps in patients with known or suspected colonic disease. Published economic evaluations are reviewed, and the structure and inputs of the economic model used to estimate cost-effectiveness and budget impact are summarized. The results of the economic analyses are presented for the colon capsule endoscopy versus computed tomographic colonography, and the budget impact of implementing the colon capsule is estimated.

Health Quality Ontario conducts full evidence-based analyses, including economic analyses, of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate it is to examine proposed health technologies in the context of available evidence and existing clinical practice, and to provide advice and recommendations to Ontario health care practitioners, the broader health care system, and the Ontario Ministry of Health and Long-Term Care.

DISCLAIMER: Health Quality Ontario uses a standardized costing method for its economic analyses. The main cost categories and associated methods of retrieval from the province's perspective are described below.

Hospital costs: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency department visit, and day procedure costs for the designated International Classification of Diseases diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in the estimated costs of the diagnoses and procedures under consideration. Due to difficulties in estimating indirect costs in hospitals associated with a particular diagnosis or procedure, Health Quality Ontario normally defaults to a consideration of direct treatment costs only.

Non-hospital costs: These include physician services costs obtained from the Ontario Schedule of Physician Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible, or from the device manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied (to both costs and effects/QALYs), as recommended by economic guidelines.

Downstream costs: All reported downstream costs are based on assumptions of population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates of funding and prices. These may or may not be realized by the Ontario health care system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach.

The economic analysis represents ***an estimate only***, based on the assumptions and costing methods explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers may be rounded to the nearest decimal point, as they may be reported from an Excel spreadsheet.

Objectives of Analysis

The objectives of this analysis were to determine the cost-effectiveness and budgetary impact of colon capsule endoscopy for the identification of polyps and colorectal cancer in patients with known or suspected colonic disease. The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Clinical Need and Target Population

Description of Disease/Condition

Colorectal cancer is a cancer in the colon or rectum. When normal cells that form the lining of the colon begin to grow abnormally, a small precancerous growth, or polyp (also referred to as an adenoma), can form. Most colorectal cancers develop from these precancerous polyps. (1)

Colorectal polyps can be noncancerous and asymptomatic. Only dysplastic polyps have malignant potential. Adenoma size affects both the histology and degree of dysplasia. Larger polyps are more likely to carry villous components and to become dysplastic. It is estimated that 1% to 5% of adenomatous polyps progress to invasive cancer if they are larger than 10 mm in diameter or high-grade dysplastic. (2) Polyps larger than 10 mm are classified as advanced adenomas, and polyps less than 5 mm are generally classified as diminutive. (3) Since progression from normal mucosa to invasive cancer can take up to 10 to 15 years, early diagnosis and removal of precancerous polyps is highly effective in preventing the development of colorectal cancer. (4, 5)

Patients with known or suspected disease of the colon, and who are symptomatic, are recommended to undergo an immediate colonic examination by colonoscopy. Patients from the same population, who are asymptomatic, are recommended to undergo regular screening by colonoscopy and sigmoidoscopy. (3)

Colonoscopy is the current gold standard for the diagnosis of colorectal polyps or neoplasia. However, the procedure is invasive, requires sedation, and has the potential for complications, including bleeding and perforation of the bowel wall, which can be dangerous and expensive to treat. Colon capsule endoscopy has been proposed as a non-invasive alternative or complementary method to colonoscopy for the detection of colorectal polyps.

Patient compliance in undergoing colonoscopy is largely impacted by concerns regarding the associated complications of the procedure. Relatively low compliance rates, varying from 10% to 26%, have been reported by colorectal cancer screening programs. (6, 7)

Prevalence and Incidence

Colorectal cancer is the third most prevalent cancer in Canada. (8) It is the second leading cause of cancer deaths in men and women combined. (9) It was estimated that in 2014, a total of 24,400 Canadians would have colorectal cancer and 9,300 would die from the disease. (10) Colorectal adenomas are found in 11% to 44% of patients who are at average risk for colorectal cancer, and the rates are higher in a population at high risk. (11, 12)

Ontario has one of the highest rates of colorectal cancer in the world. According to the Colorectal Cancer Screening Program of Ontario, 8,700 Ontarians were estimated to have colorectal cancer in 2013 and 3,350 Ontarians died from it. (13)

Ontario Context

In Ontario, conventional colonoscopy is the standard procedure for detecting colorectal lesions. For patients who have contraindications, refuse a colonoscopy, or have had an incomplete colonoscopy, virtual colonoscopy is offered; the most common approach is computed tomographic (CT) colonography. Both colonoscopy and CT colonography are currently funded under the Ontario Health Insurance Plan (OHIP).

Interventions Under Evaluation

Colon capsule endoscopy is a new diagnostic technology for colonic investigation. It is a minimally invasive way of examining the colon and does not require sedation. Patients can continue normal daily activities immediately following the procedure.

In 2006, Given Imaging Ltd. (Yoqneam, Israel) launched its first generation of colon capsule endoscopy, PillCam COLON. It is a capsule designed to be ingested by patients to take images of the colon as it passes through the gastrointestinal tract. Each side of the capsule is equipped with a camera and an automatic light-emitting diode (LED). Images captured are transferred from the device to a computer that uses RAPID (Given Imaging Ltd.), a software package designed to compile the results for review.

A systematic review showed suboptimal sensitivity and specificity of PillCam COLON for the detection of significant colorectal polyps (a polyp at least 6 mm in size or at least three polyps of any size). (14) To improve diagnostic accuracy, Given Imaging Ltd. developed a second generation of colon capsule endoscopy, PillCam COLON 2, and launched the product in 2010.

Implications in Colorectal Cancer Screening

The literature search performed for the clinical evidence-based analysis did not identify any clinical study that directly investigated colon capsule endoscopy in the setting of colorectal cancer screening. (15) Based on simulation data, it was estimated that a colon capsule endoscopy–based colorectal cancer screening program was substantially more costly than a colonoscopy-based program, when considering the costs for (a) initial procedures, (b) subsequent polypectomies given positive findings, and (c) missed cases. (14) The same study projected that colon capsule endoscopy was cost-effective only when there was a 30% increase in compliance. (14)

Colon capsule endoscopy has been proposed as a complementary test for detecting colorectal polyps, in patients who have contraindications to colonoscopy, have had a previous incomplete colonoscopy, or have refused the procedure. In Canada, the most common alternative test for this population is CT colonography. The Canadian Association of Gastroenterology updated its position statement on colorectal cancer screening in 2010. (16) The new statement endorsed the use of CT colonography for colonic areas that were not visualized endoscopically. At the same time, the association raised concerns regarding the low sensitivity of CT colonography for detecting polyps smaller than 5 mm and the radiation risk associated with CT colonography. It was reported that polyps smaller than 5 mm were not detected reliably by CT colonography. (16) A study looking at the impact of American College of Radiology recommendations on CT colonography scan results indicated that 33% of screening patients (age ≥ 50 years) with high-risk adenoma findings (confirmed with colonoscopy) would have had their CT colonography results interpreted as normal. (17)

A previous evidence-based analysis conducted by Health Quality Ontario showed that the use of CT colonography was associated with an additional risk of developing cancers incurred by the radiation exposure from the procedure itself. (18) The Canadian Association of Gastroenterology considered colon capsule endoscopy as an option for colorectal cancer screening but did not make any recommendation because of limited evidence from contemporary comparative studies. (16)

Owing to the lack of comparative studies between colonoscopy and colon capsule endoscopy, our economic analysis focuses on the use of colon capsule endoscopy as an alternative for patients referred for CT colonography. The analysis examines two cohorts: the entire patient population referred for CT colonography, and the subpopulation of patients who had an incomplete colonoscopy within the year prior to their CT colonography procedure. For further discussion of these cohorts, see the clinical evidence-based analysis. (15)

Research Question

What is the cost-effectiveness and 1-year budgetary impact of colon capsule endoscopy for the detection of colorectal polyps and cancer?

ECONOMIC LITERATURE REVIEW

Research Methods

Literature Search

We performed an economic literature search using Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, Ovid EMBASE, Wiley's Cochrane Library (Issue 4 of 4 Oct 2013), and HEED, for studies published from January 1, 1998, to November 27, 2013. A single reviewer reviewed the titles and abstracts, and we retrieved the full-texts of all potentially relevant articles. The reviewer also reviewed the reference lists of all full-text articles to identify any additional studies that may not have been identified in the original search. The literature search strategy is presented in Appendix 1.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 1998, and November 27, 2013
- Full economic evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses
- Cost-minimization studies
- Economic evaluations reporting incremental cost-effectiveness ratios (ICERs) (i.e., cost per quality-adjusted life-year [QALY]/life-years gained [LYGs], cost per event avoided, or cost per case detected)
- Studies including colon capsule endoscopy

Exclusion Criteria

- Narrative reviews
- Editorials
- Studies involving paediatric populations
- Abstracts, posters, reviews, letters/editorials, foreign-language publications, unpublished studies

Results of Economic Literature Review

We identified a total of 171 citations; after the title and abstract review, 164 articles were excluded. We attempted extraction of the full texts of the remaining seven articles, and collected six articles. (19-24) We extracted the data from the six articles for a more detailed review.

We excluded two studies as they were not economic evaluations (19, 20) and one because it did not include colon capsule endoscopy in the analysis. (23) Three articles met the inclusion criteria. The included studies were two cost-effectiveness analyses (21, 22) and a cost analysis, (24) conducted from both societal (22, 24) and third-payer (21) perspectives.

One of two cost-effective analyses identified through the systematic review was a US study by Hassan et al (22) that compared colon capsule endoscopy and colonoscopy in a colorectal cancer screening context for patients aged 50 to 80 years who were at average risk for colorectal cancer. Patients were assumed to be screened every 10 years for both strategies,

and the study took a societal perspective of secondary care in the United States. Patients were examined until end of life using a Markov model based on effectiveness, from the published literature, with estimates for base case analysis selected in consultation with a principal investigator and an expert panel.

The authors concluded that the cost-effectiveness of colon capsule endoscopy was associated with its potential to promote compliance to screening. Colon capsule endoscopy with a 6 mm polyp threshold for referral for post–colon capsule endoscopy polypectomy via colonoscopy resulted in 8,927 discounted life-years saved. Without a 6 mm threshold, colon capsule endoscopy resulted in 8,255 life-years saved. Colonoscopy resulted in 10,699 life-years saved. Costs were $465 million, $412 million, and $377 million, respectively. Colonoscopy dominated colon capsule endoscopy as it was less costly and more effective when a 6 mm threshold for post–colon capsule endoscopy polypectomy was used. Colon capsule endoscopy became more cost-effective than colonoscopy when the compliance rate for colonoscopy was at least 30% less than that for colon capsule endoscopy. (22)

The second cost-effective analysis, also from Hassan et al, (21) compared various screening strategies: no screening, colonoscopy every 10 years, colon capsule endoscopy every 5 or 10 years, sigmoidoscopy every 5 or 10 years, and fecal immunochemical testing every 1 or 2 years. The analysis was conducted for average-risk patients in France and observed patients for their lifetime. A third-payer perspective was adopted for costs. In the base case analysis, fecal immunochemical testing performed every year was the most cost-effective option, with an ICER of €48,165 per life-year gained (LYG) versus fecal immunochemical testing performed every 2 years, which was the next most cost-effective option. Although colon capsule endoscopy every 5 years was as effective as fecal immunochemical testing annually, it was not cost-effective. In contrast to the Canadian setting, colonoscopy in France is performed with sedation, increasing costs substantially. When the anaesthesia cost was omitted, all fecal and sigmoidoscopy programs became cost-saving compared with no screening, owing to a reduction in costs of follow-up polypectomies. Also, when colorectal cancer treatment costs were increased to reflect recent biological therapy options, guaiac fecal occult blood test every 2 years was the only cost-saving strategy. Furthermore, when the cost of colonoscopy without anaesthesiologist assistance was used (in addition to increased colorectal cancer treatment costs), all screening strategies were cost-saving except for colon capsule endoscopy.

A cost analysis performed by Wohl et al (24) used a theoretical model based on Markov chains to compare fecal occult blood test, colon capsule endoscopy, once-lifetime colonoscopy, twice-lifetime colonoscopy, and no screening for the general population aged 50 to 75 years. The study was set in outpatient care in the Czech Republic, with no explicitly stated perspective. The time horizon was up to the age of 75 years, with clinical and effectiveness data coming from the published literature and the authors' assumptions. The authors reported the costs of the individual screening programs based on only one previously published study. The authors concluded that twice-lifetime colonoscopy, with the first colonoscopy at age 50 years and the second at age 59, was the best screening option for colorectal cancer. Compared with the costs of twice-lifetime colonoscopy, the costs of colon capsule endoscopy were nearly double.

Wohl et al (24) did not state how the studies for clinical and effectiveness data were identified or whether a systematic review of literature was undertaken. Costs and outcomes of different interventions were not compared head to head, and no incremental analysis was performed; therefore, it is not possible to determine the most cost-effective option. Given this, and the unclear methods, the results should be interpreted with caution.

The results of the literature review demonstrate that colon capsule endoscopy use for colorectal cancer screening is expensive and not cost-effective overall, but may be cost-effective if compliance to screening programs is increased through the adoption of this technology, and if long-term downstream costs are taken into account. None of the included studies were directly relevant to the Ontario context as they were conducted outside of Canada. Therefore, we conducted a primary cost-effectiveness analysis and a budget impact analysis, both described below.

PRIMARY ECONOMIC ANALYSIS

Cost-Effectiveness Model

We conducted a cost-effectiveness analysis to estimate the incremental costs and outcomes (life-years lost) of diagnostic interventions due to misdiagnoses in the identification of advanced colorectal polyps. The diagnostic accuracy of each test was determined by the clinical evidence-based analysis conducted by Health Quality Ontario. (15) The additional costs and outcomes included were:

- Unnecessary colonoscopy due to a false-positive result
- Cancer treatment costs due to a false-negative result

A Markov model was developed to track the natural history of colorectal cancer progression and then to determine the incremental costs and life-years saved between a false-negative result and true-positive result. In this case, a false-negative result would result in patients entering the model in the health state of "advanced adenoma," whereas a true-positive result would result in patients entering the model in the health state "healthy, no adenoma," but with an increased risk of developing further polyps due to their history.

Interventions Evaluated

Colon capsule endoscopy was compared with CT colonography for the detection of advanced colorectal polyps (> 10 mm).

Target Population

The target population of this economic analysis was patients aged 18 to 100-plus years who had been referred for CT colonography for known or suspected colonic disease. The analysis focuses on patients with advanced colorectal polyps (> 10 mm) because the larger polyps carry a more immediate impact on health compared with intermediate polyps (≤ 6 mm); misdiagnoses of non-advanced polyps would have limited impact in terms of their developing into larger polyps or colorectal cancer.

Data obtained from the Institute for Clinical Evaluative Sciences (ICES) included the number of CT colonography procedures performed and the age of patients referred. The Institute for Clinical Evaluative Sciences is an independent non-profit research organization that acts as a large repository for annually updated, de-identified, individual-level health administrative data. Disease-specific cohorts can be created using health administrative case definitions that link hospital in-patient and outpatient care, physician claims, and drug benefits data over time.

Table 1 shows the number of procedures performed by age, with the calculated weight and final weighted average age, based on the mid-point of each age grouping. Through this calculation, the average age of patients entering the model is 67 years.

Table 1: Number of Computed Tomographic Colonographies by Patient Age, in Ontario, 2012

Age Group (y)	No. of CTC Procedures
18–29	37
30–39	100
40–49	452
50–54	643
55–59	780
60–64	855
65–69	1,138
70–74	1,012
75–79	906
80–89	1,128
90+	111
Weighted age[a]	**67**

Abbreviations: CTC, computed tomographic colonography.
[a]Weighted average age of patients entering the cost-effectiveness model.
Source: Data from the Institute for Clinical Evaluative Sciences, 2014.

Perspective

The primary analytic perspective was that of the Ministry of Health and Long-Term Care. Costs from this perspective included direct procedure costs described by the Ontario Case Costing Initiative (OCCI), physician fees for services covered by provincial fee schedules, and the cost of the capsule itself as provided by a manufacturer.

All costs are reported in 2014 Canadian dollars.

Discounting and Time Horizon

An annual discount rate of 5% was applied to both costs and life-years lost, as recommended by economic guidelines in Canada. A lifetime time horizon was used in the analysis.

Variability and Uncertainty

We conducted a one-way sensitivity analysis to test the robustness of the results to variations in model parameters. The following model parameters were varied:

- Cost of colon capsule endoscopy and CT colonography
- Sensitivity of colon capsule endoscopy and CT colonography
- Specificity of colon capsule endoscopy and CT colonography
- Prevalence of advanced adenomas in the patient population

Model Structure

A decision tree was constructed to evaluate the costs and outcomes for each testing strategy, as seen in Figure 1. The parameters that informed the branch probabilities, including the sensitivity, specificity, and diagnostic accuracy of both procedures, were taken from the companion clinical evidence-based analysis. (15)

The model enabled us to calculate the incremental cost and outcomes for misdiagnoses. False-positive results carried the added cost of unnecessary colonoscopies. False-negative results placed patients at higher risk of developing colorectal cancer, which would incur treatment costs and increased mortality.

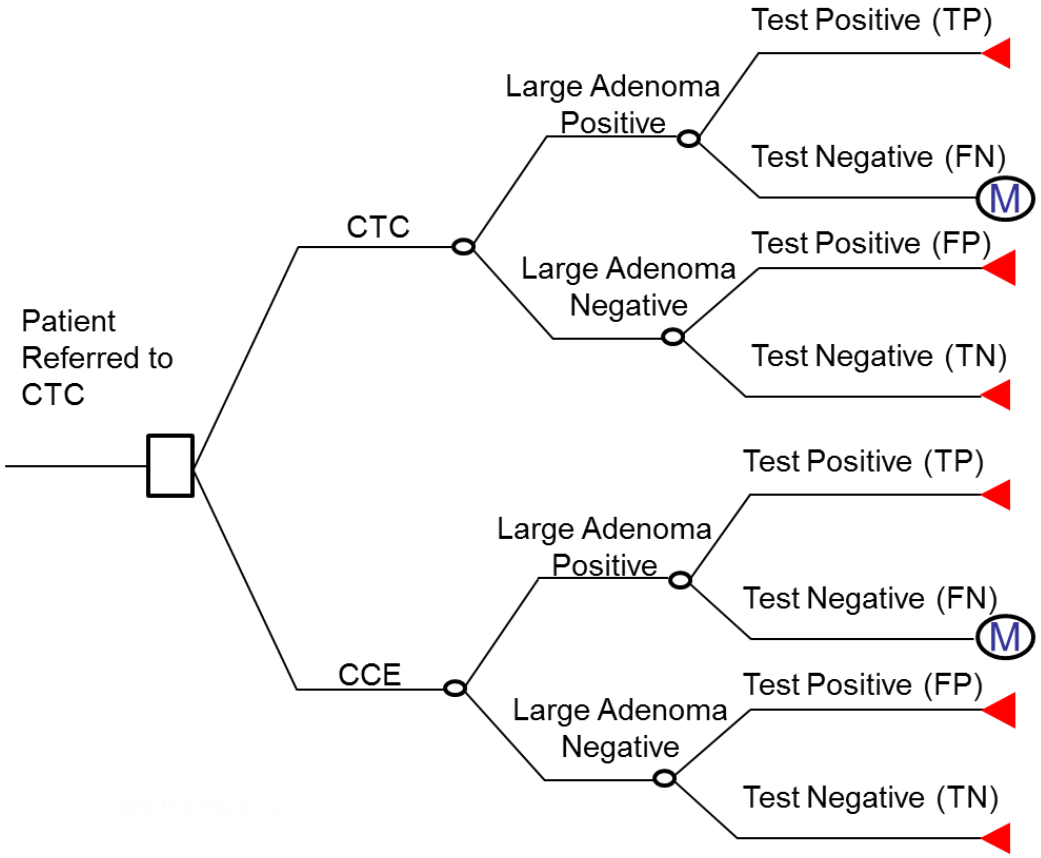

Figure 1: Decision Tree for Patients Referred for Computed Tomographic Colonography

Abbreviations: CCE, capsule endoscopy; CTC computed tomographic colonography.

A Markov model was used to examine the additional costs due to false-negative results. The overall structure of the model, including the transitions between health states, is presented in Figure 2. The circles in the diagram represent different health states, and arrows show the possible patient transitions in a given model cycle. Arrows labelled *Surveillance Detection* indicate that patients had polyps or preclinical colorectal cancer identified through CT colonography surveillance, which occurred every 5 years. This surveillance is not included in the natural history model. Although not shown, all health states except for symptomatic and cancer treatment were susceptible to death from natural causes, which is another absorbing health state from which patients could not transition from in future cycles.

Analyses were conducted in Microsoft Excel 2013.

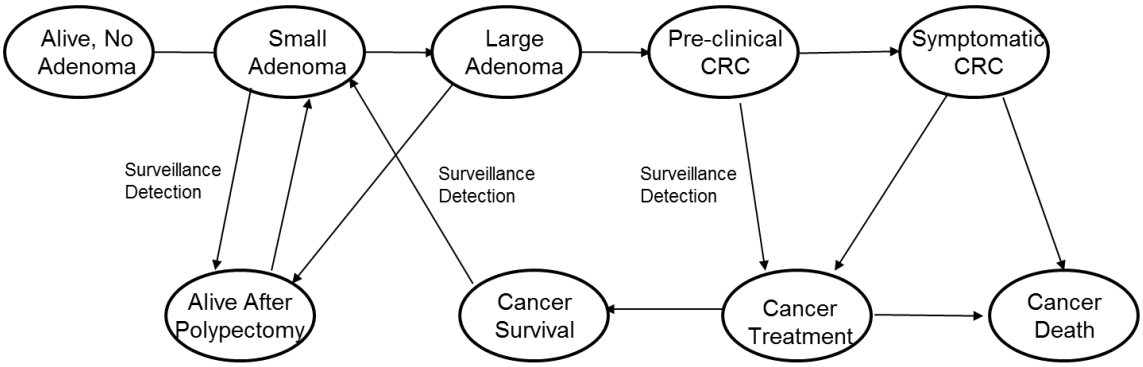

Figure 2: Long-Term Markov Model

Abbreviation: CRC, colorectal cancer.

Model Input Parameters

Clinical Model Input Parameters

The basic model structure and inputs are adapted from a recent Canadian model for colorectal cancer screening developed by Heitman et al. (25) A number of different input parameters were used to populate the model. These include variables used to model the natural history of the disease, and variables that modify the natural history model to account for treatment effects and costs of the intervention. Increased false-positives were modelled according to the relative diagnostic accuracy of colon capsule endoscopy and CT colonography.

Natural History Model Input Parameters

Several input parameters were used to model the natural history of colorectal cancer (Table 2):

- Prevalences of non-advanced and advanced polyps
- Prevalence of colorectal cancer
- Distribution of colorectal cancer by stage
- Mortality due to cancer
- All-cause age-dependent mortality
- Costs of cancer treatment

The annual probability of dying from cancer was calculated based on the 5-year mortality rates from the American Joint Committee on Cancer. (26) To account for increased mortality over time, the absolute difference between the annual probability of dying from cancer and the annual probability of death from age 50 was applied to each subsequent year. (27) This was done because the natural history model was adapted from Heitman et al's model, which examined colorectal cancer screening in Canadian patients aged 50 to 74 years and which used static mortality risk for colorectal cancer and for other natural causes. To expand our model to a lifetime time horizon, we used life tables as the risk of dying from other natural causes became an important factor. Cancer mortality risk was conservatively assumed to follow the same pattern. The natural history model begins at age 50 in order to validate it for ages 50 to 74 against the model by Heitman et al.

The prevalences of advanced polyps and of colorectal cancer are based upon a systematic review and meta-analysis performed by Heitman et al. (28) The distribution of cancer between the four different stages was based on a combination of clinical trials of the fecal occult blood test. (25) The costs of cancer treatment were determined by Heitman et al based on local information from Calgary and a combination of other studies. (25)

Table 2: Natural History Model Inputs

Model Parameter	Value	Range (%)	Source
Prevalence (age 50 y)			
Advanced polyps	3.8%	2.0–5.0	Heitman et al (28)
Non-advanced polyps	17.1%	10–25	Heitman et al (28)
CRC	0.10%	0.005–0.20	Heitman et al (28)
Transition probabilities			
No polyp to non-advanced polyp (no history of adenoma or CRC)	2.0%	1.0–3.0	Heitman et al (25)
No polyp to non-advanced polyp (history of adenoma or CRC)	3.8%	3.0–5.0	Heitman et al (25)
Non-advanced adenoma to advanced adenomas	1.0%	1.0–3.0	Heitman et al (25)
Mortality			
All causes	Age-dependent, Statistics Canada probabilities		Statistics Canada (27)
Cancer			O'Connell et al (26)
Stage I	1.113%		
Stage II	3.483%		
Stage III	9.573%		
Stage IV	39.223%		
CRC stage distribution			
Stage I	14.5%	12–25	O'Connell et al (26)
Stage II	35.6%	34–39	O'Connell et al (26)
Stage III	28.0%	23–32	O'Connell et al (26)
Stage IV	21.9%	18–25	O'Connell et al (26)
Diagnostic tools			
Colonoscopy sensitivity for CRC	96.6%		Hixson et al, (29) Rex et al, (30) Bressler et al (31)
Cancer treatment costs			
Stage I	$27,706		Heitman et al (25)
Stage II	$39,976		Heitman et al (25)
Stage III	$107,031		Heitman et al (25)
Stage IV	$148,227		Heitman et al (25)

Abbreviations: CRC, colorectal cancer.

Validation

In an effort to validate the results for the natural history model, the number of cancer cases, cancer-related deaths, and life-years lived projected from the model were compared with those in recent Canadian and American models. Table 3 shows the results for the constructed model versus the model presented in Heitman et al, (25) which served as the basis for our model. The results are compared for natural history of patients between the ages of 50 and 75, with very close agreement. Another recent Canadian model by Telford, which observes patients until death and has similar assumptions, is also compared. (32) Finally, a number of American natural history models are compared, including the Harvard model, (33) Microsimulation Screening Analysis (MISCAN) model, (34, 35) Vanderbilt model, (36) and those of Ladabaum et al (37, 38) and Vijan et al, (39) as reported by the US Institute of Medicine. (40) The difference in model results is expected because of the different underlying structures and assumptions.

The model developed to compare colon capsule endoscopy and CT colonography matches closely with that of Heitman et al, whereas it has a slightly increased number of cancer cases predicted and cancer deaths than found by Telford et al. (32) The average calculated life expectancy at 50 years of age determined by our model is slightly higher than that in the American models presented, indicating a relative underestimation of cancer mortality in the constructed model and, by extension, the other Canadian models presented.

Table 3: Validation of Natural History Model

Model	Cancer, N	Cancer Deaths, N	Average Calculated Life Expectancy at Age 50 Years
Model in current study			29.70
Ages 50–75 y	4,561	1,952	
Lifetime	7,185	4,042	
Heitman et al[a] (25)	4,857	1,782	
Telford et al[b] (32)	6,257	3,814	
Harvard (33)			25.12
Ladabaum et al (37, 38)			27.23
MISCAN (34, 35)			27.29
Vanderbilt (36)			27.39
Vijan et al (39)			25.07

Abbreviations: MISCAN, Microsimulation Screening Analysis; N, number.
[a]Model gives results for cohort of aged 50 to 75 years.
[b]Model gives results for cohort of patients from 50 years old until death.

Prevalence

The prevalence of advanced colorectal polyps in the patient population referred for CT colonography is based on prevalence rates taken from the literature and expert opinion. A range of prevalence rates is reported in the literature, with rates generally reported for the average-risk population at age 50 years. The base rate uses a prevalence of advanced adenomas of 7%, based on an average-risk population as reported by Betés Ibáñez et al, (11) whose study of 2,296 patients was the largest identified that reported prevalence rates. Based on expert opinion, this estimate of prevalence and that used in Heitman et al's study for the age group 65 to 75 (8.2%) were both conservative for the Ontarian population. (25) In our sensitivity analysis, we varied the prevalence from the lowest rate reported for 50-year-old patients (3%) (28) up to

15%, which is an upper estimate of prevalence for the patient population referred for CT colonography, including those with prior incomplete colonoscopies.

Resources and Cost Model Input Parameters

The costs of colon capsule endoscopy and CT colonography were calculated by incorporating costs from a number of sources:

- The cost of the capsule itself, obtained from the manufacturer
- Professional fees associated with the procedures
- Direct costs captured through the OCCI database. These direct costs include direct medical costs (i.e., procedure, pathology, physician, nursing, diagnostic imaging, pharmacy, and laboratory costs) and hospital overhead costs (e.g., those for administration, finance, human resources, and plant operations)

Complication rates are also included in the analysis, based on studies identified through the clinical evidence-based analysis, (15) as shown in Table 4. (41-44) For colon capsule endoscopy, complications included are the rates of capsule retention and technical failure; for CT colonography, they are perforation from air insufflation and radiation risk. These rates are incorporated into the weighted average costs in this analysis.

Table 4: Complication Rates Used in Model

Adverse Event	CCE, %	CTC, %
Retention	0.80	—
Technical failure	1.40	—
Perforation	—	0.050
Increased lifetime risk of cancer development	—	0.044

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography.
Sources: CCE data from Hassan et al, (21) Eliakim et al, (41) and Hagel et al. (42) CTC data for radiation risk from Leddin et al (16) and for perforation from Health Quality Ontario. (18)

Table 5 and Appendix 2 present the costs relating to both colon capsule endoscopy and CT colonography, including complications and associated costs. Costs for both procedures include professional fees for an initial assessment, direct costs captured through OCCI, the cost of the capsule itself, and costs related to complications. The weighted average cost of colon capsule endoscopy is $1,120.42 and of CT colonography is $746.20.

Table 5: Costs of Colon Capsule Endoscopy and Computed Tomographic Colonography, Including Costs for Complications

Resource Item	Cost, $	Data Sources and Comments
CCE		
Capsule	650.00	Cost of colon capsule, as provided by lead manufacturer Given Imaging. Assumption: all workstations, wireless belts, and software are covered by manufacturer, as is current practice
Partial assessment	38.05	OSB A418 partial assessment (gastroenterology), (45) consultation, and visits, as suggested by expert panel
Direct costs	204.00	Assumption: direct cost will be equal to that of the small-bowel capsule, captured in OCCI database (46)
Interpretation of data	183.38	Assumption: price to assess the data after the procedure will be 1.5 times the price of the small-bowel capsule (OSB G332) (45) due to increased reading time
Complications		
Technical failure	425.23	Costs include direct costs and partial assessment for 2 procedures, and the cost of 1 capsule and 1 interpretation of results
Double-balloon enteroscopy—capsule retention	1,490.37	See Appendix 2 for detailed costing. Endoscopy assumed to be used in 12.5% of capsule retrievals (47)
Surgery—capsule retention	10,374.85	Cost of small-bowel capsule retrieval (48) converted to 2014 $ CAD. Surgery assumed to be used in 58.7% of capsule retrievals (47)
Weighted average cost	1,120.42	Based on 2.4% retention rate, 3.7% technical failure (assumed independent)
CTC		
Partial assessment	38.05	OSB A418 partial assessment (gastroenterology), (45) consultation and visits, as suggested by expert panel
Direct costs	441.00[a]	Weighted average of direct costs from OCCI for CCI codes 2.NK.70.BA-BL and 2.NK.71.BA-BL, inspection and biopsy of small bowel with gastroscope
Interpretation of results	235.30	OSB X234 CTC (45)
Complications		
Perforation	31,223.00	Cost for perforation assumed equal to that for colonoscopy perforation given in Heitman et al (25)
Radiation risk: development of cancer	38,440.00	Lifetime CRC treatment costs as estimated with SEER-Medicare data, (49) converted and inflated to 2014 $ CAD
Weighted average cost	746.20	Based on: • 0.004% increased lifetime risk of cancer (16) • 0.05% risk of perforation from air insufflation (18)

Abbreviations: CCE, colon capsule endoscopy; CCI, Canadian Classification of Health Interventions; CRC, colorectal cancer; CTC, computed tomographic colonography; OCCI, Ontario Case Costing Initiative; OSB, Ontario Schedule of Benefits; SEER, US National Cancer Institute's Surveillance, Epidemiology and Results Program.

[a]Direct costs for CTC unavailable from OCCI because of low number of procedures captured. Costs assumed to be equal to "CT abdomen" procedures.

The sensitivity and specificity of both colon capsule endoscopy and CT colonography are provided in Table 6, based on the clinical evidence-based analysis. (15) These values are used to generate the estimated number of false-positive and false-negative test results.

Table 6: Sensitivity and Specificity of Colon Capsule Endoscopy and Computed Tomographic Colonography

	Accuracy ≥ 10 mm for CCE		Accuracy ≥ 10 mm for CTC		
	%	95% CI, %	%	95% CI, %	*P* Value
Sensitivity	92.8	64–100	78.6	49–94	.26
Specificity	91.6	76–98	91.7	76–98	.99

Abbreviations: CCE, colon capsule endoscopy; CI, confidence interval; CTC, computed tomographic tomography.

Cost-Effectiveness Analysis Results: Base Case Analysis

False-Positive Results

The specificities of colon capsule endoscopy and CT colonography are used to calculate the additional false-positive results generated by colon capsule endoscopy, which incur the additional cost of an unnecessary confirmatory colonoscopy. The original costs of each procedure, number of false-positive cases, and additional cost per patient with a false-positive result are presented in Table 7. The cost for additional false-positives is $0.41 for colon capsule endoscopy (see Appendix 2 for the costing of colonoscopy).

Table 7: Economic Model Base Case—False-Positive Results

Strategy	FP	Additional FP	Cost of Unnecessary Colonoscopy	Incremental Cost Due to FP
CTC	0.07719	—	—	—
CCE	0.07812	0.00093	$438.95	$0.41

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography; FP, false-positive.

False-Negative Results

The sensitivities of colon capsule endoscopy and CT colonography are used to calculate the false-negative results generated by CT colonography, which incur the additional cost of cancer treatment. With patients entering the model in the “large adenoma” health state owing to false-negative results, they are further along the adenoma-carcinoma sequence than are patients with true-positive results who enter the model as “alive after polypectomy” and have to pass through the “small adenoma” health state before reaching the “large adenoma” state. Table 8 demonstrates the cost per false-negative case avoided from the economic model. The original cost of each procedure, number of false-negative results, additional false-positive results generated by CT colonography, and resulting incremental cost per patient are shown.

Table 8: Economic Model Base Case—False-Negative Results

Strategy	FN	Additional FN	Cost of Cancer Treatment per Patient[a]	Incremental Cost Due to FN
CTC	0.01498	0.00994	$11,697	$116.27
CCE	0.00504	—	—	—

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography; FN, false-negative.
[a]Result from Markov model.

Table 9 presents the total costs for colon capsule endoscopy and CT colonography with additional false-negative and false-positive results per patient incorporated, along with the incremental cost for colon capsule endoscopy, the number of LYGs by avoiding false-negative results with use of colon capsule endoscopy, and the resultant incremental cost per LYG.

Table 9: Economic Model Base Case—Overall Results

		Incremental		
Intervention	Total Cost, $ (Test + Cost of FN and FP)	Cost, $	LYGs by FN Avoided	ICER $/LYG
CTC	862.47	–	—	Reference
CCE	1,120.83	258.36	0.000966	**26,751**

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography; FN, false-negative; FP, false-positive; ICER, incremental cost-effectiveness ratio; LYG, life-year gained.

Sensitivity Analysis

A one-way sensitivity analysis was conducted on key model parameters, as described below, with results summarized in Table 10.

Sensitivity of Colon Capsule Endoscopy and of Computed Tomographic Colonography

The model is highly dependent upon the difference in sensitivity between colon capsule endoscopy and CT colonography to derive the estimated number of patients entering the false-negative arm, which results in the largest contribution of additional costs for a misdiagnosis and generates the LYGs by the more sensitive technology. Due to the uncertainty surrounding the underlying clinical data, the impact of decreasing the sensitivity of colon capsule endoscopy and increasing the sensitivity of CT colonography was explored to examine the variation in the model results. The final ICER value was highly responsive to changes in sensitivity in either diagnostic test. Decreasing the sensitivity of colon capsule endoscopy from 92.8% to 85% resulted in the incremental cost per LYG rising to about $74,000. Increasing the sensitivity of CT colonography from 78.6% to 85% resulted in the ICER value reaching almost $61,000.

Specificity of Computed Tomographic Colonography

The specificity of CT colonography was increased to the maximum value of the range given in the clinical study (15) in order to investigate the additional cost related to more false-positive results generated by colon capsule endoscopy. This increase from the base case of a specificity of 91.7% to 97.8% resulted in an increased ICER of about $29,300. As expected, the ICER was

not as sensitive to changes in specificity as false-positives bear a much lower cost impact than false-negatives.

Price of Capsule Unit

The sensitivity to variations in the price of the capsule itself was explored. As the manufacturer incorporates the cost of workstations, sensor belts, and proprietary software into the average cost of the capsule, this could increase or decrease depending on diffusion and individual contracts. We tested the impact of a 15% fluctuation in price. When the price of the capsule was inflated to $747.50, the resulting ICER was almost $36,900; when it was decreased to $552.50, the ICER was about $16,700.

Proportion of Capsule Retentions Resolved Surgically

The impact of increasing the proportion of capsule retentions resolved surgically was explored by increasing from the base case of 58% to 100% to determine the maximum impact additional surgeries could have on estimated cost-effectiveness. This resulted in an ICER of $30,300.

Proportion of Patients Treated With Chemotherapy

Current information from the Cancer Quality Council of Ontario indicates that for stage III cancer, 55% of patients aged 65 years and older are treated with any guideline-recommended chemotherapy, with significantly lower rates in patients over age 80. (50) In fact, for those aged 65 to 70 and 71 to 80 years, the use of any guidelines-recommended chemotherapy is 72% and 65%, respectively. After age 80, the rate falls to 29%. When we used these age-specific treatment rates for all stages of cancer, the ICER became almost $31,000.

Prevalence of Advanced Adenomas

Finally, the results were found to depend heavily on the prevalence of advanced polyps in the patient population. A wide range of prevalence rates were tested, with 7% chosen as a conservative estimate for the population referred for CT colonography, based on expert advice. This assumption is also deemed conservative based on the fact that the average age of a patient referred for CT colonography is 67 years, with other models differentiating between patient cohorts aged 50 to 64 and 65 to 75 to account for the increased risk in older populations. After decreasing the prevalence to 3%, the lowest prevalence rate found for average-risk patients aged 50 years old, (32) the ICER increased to almost $78,500. As the prevalence was increased, the ICER dropped steadily, reaching almost $6,100 at a prevalence rate of 15%.

Table 10: Sensitivity Analysis—Cost-Effectiveness Model

Parameter	Base Case Value	Sensitivity Analysis Value	Incremental Changes		
			Cost of CCE, $	Misdiagnoses by CTC, %	ICER ($/LYG) for CCE
Base case results			**258.36**	**0.901**	**26,751**
Sensitivity of CCE	92.8%	92.0%	264.91	0.845	29,067
		90.0%	281.29	0.705	36,278
		85.0%	322.23	0.355	74,025
Sensitivity of CTC	78.6%	80.0%	270.70	0.803	31,316
		85.0%	313.13	0.453	60,957
		90.0%	353.18	0.103	196,297
Specificity of CTC	91.7%	97.8%	283.26	(4.772)	29,329
Price of capsule unit	$650	$747.50	355.86	0.901	36,846
		$552.50	160.86	0.901	16,656
Proportion of capsule retentions resolved surgically	58%	100%	292.64	0.901	30,300
Proportion of patients treated with chemotherapy	All	Age-dependent		0.901	30,994
Prevalence of advanced adenomas	7%	3%	258.36	0.329	78,474
		5%	258.36	0.615	42,268
		10%	258.36	1.330	15,113
		15%	258.36	2.045	6,062

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography; LYG, life-year gained.

BUDGET IMPACT ANALYSIS

Several economic evaluations identified in the literature review addressed colorectal cancer screening from a cost-effectiveness perspective. However, none of the studies were relevant to the Ontario health system or the expected place in therapy of colon capsule endoscopy as determined through expert consultation. In addition, none of the reports dealt with the budgetary impact of colon capsule endoscopy implementation. Due to these limitations, we conducted a primary budget impact evaluation.

Research Methods

Type of Analysis

We conducted a descriptive cost analysis to estimate the 1-year costs associated with increased uptake of colon capsule endoscopy as an alternative to CT colonography for two groups of patients:

1. All patients referred for CT colonography
2. The subpopulation of patients who had an incomplete colonoscopy within the previous year

Perspective

The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Model Input Parameters

The number of CT colonography procedures and number of patients were derived from the Discharge Abstract Database and Same-Day Surgery Database housed at ICES. Data were captured from 2008 to 2012; these were the most recent data available.

Resource Utilization

Table 11 summarizes the number of procedures per year for 2011 and 2012 for both CT colonography and colon capsule endoscopy. The OHIP code used to capture CT colonography was established in April of 2011; therefore, prior years were not captured, and the increase in number of procedures from 2011 to 2012 may be due to the fee code becoming more commonplace. The number of colon capsules used was provided by Given Imaging, the capsule manufacturer, which noted that the first-generation capsule was sold until 2010, at which point it was replaced with the second-generation capsule. The number of incomplete colonoscopies was identified using OHIP fee codes Z555, Z499, and Z497, with E747 or E705. This method for identifying incomplete colonoscopies was developed based on a study by Shah et al (51) and through consultation with ICES analysts.

Table 11: Annual Number of Procedures for Computed Tomographic Colonography and Colon Capsule Endoscopy

Strategy	2008	2009	2010	2011	2012
CTC[a]	n/a	n/a	n/a	4,467	7,262
Incomplete colonoscopy[b]				1,912	1,969
CCE (C1/C2)[c]	30/—	23/—	0/0	4/10	—/16

Abbreviations: C1, PillCam COLON generation 1; C2, PillCam COLON generation 2; CCE, colon capsule endoscopy; CTC, computed tomographic colonography; n/a, not available.

[a]Captured via Canadian Institute for Health Information Canadian Classification of Health Interventions code 3NM20 or Ontario Health Insurance Plan fee code X234 (introduced April 1, 2011): CTC (including additional CT acquisition sequencing and/or post-processing, 2- or 3-dimensional reconstruction(s), administration of contrast, and fecal tagging, if rendered).

[b]Patients referred for CTC due to incomplete colonoscopies; data on these procedures were not collected prior to 2011.

[c]Provided by manufacturer, Given Imaging Ltd.

Sensitivity Analysis

The methods of estimation used in this analysis are subject to uncertainty because they rely on several assumptions and on data from a variety of sources. We explored all uncertain parameters in one-way sensitivity analyses over reasonably expected ranges. We varied the following parameters:

- Rate of uptake of the colon capsule
- Professional fee to interpret colon capsule data
- Complication rates for both diagnostic modalities
- Cost of surgery for capsule retrieval

Results of Budget Impact Analysis

Colon Capsule Endoscopy as Replacement for All Computed Tomographic Colonography Procedures

The total 1-year cost associated with the replacement of all CT colonography procedures in patients aged 18 years and older in Ontario is about $5.43 million. This cost represents the current annual expenditure by the health care system for the investigation of colorectal cancer and polyps for patients referred for CT colonography for incomplete colonoscopy or other reasons.

If colon capsule endoscopy were to replace CT colonography for patients aged 18 and older in Ontario, the program would cost about $8.15 million in the first year, assuming complete uptake of the capsule procedure. This would amount to an additional annual expenditure of $2.72 million, as shown in Table 12.

Table 12: Results of Budget Impact Analysis for Colon Capsule Endoscopy Replacing All Computed Tomographic Colonography Procedures

	CCE	CTC
Total cost per procedure	$1,120.42	$746.20
Incremental cost	$374	
Volume of patients in 2012	7,262	
Total cost	$8,154,400	
Budget impact versus current usage	$2,721,345	

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography.

Colon Capsule Endoscopy as Replacement for Computed Tomographic Colonography in Patients With Prior Incomplete Colonoscopies

If colon capsule endoscopy were to replace CT colonography for patients aged 18 and older in Ontario who had undergone an incomplete colonoscopy within the previous year (about 28% of those receiving a CT colonography scan for colonic polyps), the program would cost about $6.17 million in the first year, assuming complete uptake of the capsule procedure. Details are shown in Table 13. This would amount to an additional annual expenditure of about $741,000.

Table 13: Results of Budget Impact Analysis for Colon Capsule Endoscopy Replacing Computed Tomographic Colonography in Patients With Prior Incomplete Colonoscopy

	CCE	CTC
Total cost per procedure	$1,120.42	$746.20
Incremental cost	$374	
Volume of patients in 2012	1,985	5,293
Total cost	$6,173,657	
Budget impact versus current usage	$740,578	

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography.

Sensitivity Analyses

Sensitivity analyses are described below, with results reported in Table 14 (the scenario where colon capsule endoscopy replaces all CT colonography procedures) and Table 15 (the scenario where colon capsule endoscopy replaces CT colonography for patients with an incomplete colonoscopy within 1 year prior). We varied the following parameters:

- Rate of uptake of capsule procedure
- Cost for professional fees for interpretation of data (assuming the same cost as small-bowel capsule interpretation, without a 50% premium added to account for longer reading time)
- Reduced rate of capsule retention
- Proportion of capsule retention cases resolved surgically

Table 14: Results of One-Way Sensitivity Analyses—Colon Capsule Endoscopy Replacing All Computed Tomographic Colonography Procedures

Parameter	Base Case Value	Sensitivity Analysis Value	Current Expenditure	Expenditure With CCE Replacing CTC	Budget Impact (Compared With Current Practice)
Base case results[a]			**$5,433,100**	**$8,154,424**	**$2,721,345**
Capsule uptake	100%	10%	$5,433,100	$5,708,571	$275,492
		25%	$5,433,100	$6,116,213	$683,135
		50%	$5,433,100	$6,795,617	$1,362,538
		75%	$5,433,100	$7,475,020	$2,041,942
Professional fee for CCE interpretation	$183.38	$122.25	$5,432,108	$7,713,115	$2,281,007
Capsule retention	0.8%	2.6%[b]	$5,434,577	$8,835,746	$3,401,187
Proportion of capsule retention cases resolved surgically	59%	100%	$5,433,603	$8,393,056	$2,959,453

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography.
[a]Base case represents scenario where all CTC procedures are replaced with CCE.
[b]Highest retention rate reported from clinical studies identified in clinical evidence-based review. (15)

Table 15: Results of One-Way Sensitivity Analyses—CCE Replacing All CTC Procedures in Patients With Prior Incomplete Colonoscopy

Parameter	Base Case Value	Sensitivity Analysis Value	Current Expenditure	Expenditure With CCE Replacing CTC	Budget Impact (Compared with Current Practice)
Base case results[a]			**$5,433,079**	**$6,173,657**	**$740,578**
Capsule uptake	100%	10%	$5,433,079	$5,510,494	$77,416
		25%	$5,433,079	$5,621,021	$187,943
		50%	$5,433,079	$5,805,233	$372,154
		75%	$5,433,079	$5,989,445	$556,366
Professional fee for CCE interpretation	$183.38	$122.25	$5,432,108	$6,053,294	$621,186
Capsule retention	0.8%	2.6%[b]	$5,434,577	$6,359,485	$924,908
Proportion of capsule retention cases resolved surgically	59%	100%	$5,433,603	$6,238,741	$805,138

Abbreviations: CCE, colon capsule endoscopy; CTC, computed tomographic colonography.
[a]Base case represents scenario where all patients referred for CTC with prior incomplete colonoscopy are given CCE.
[b]Highest retention rate reported from clinical studies identified in clinical evidence-based review. (41)

LIMITATIONS

A number of limitations and assumptions are associated with the cost-effectiveness analysis presented. The major limitation is the uncertainty inherent in the clinical data that were used to estimate the diagnostic accuracy of colon capsule endoscopy and CT colonography. (43) Although that study suggests that colon capsule endoscopy is more sensitive than CT colonography to detect advanced adenomas, the results were not statistically different. This casts a great degree of uncertainty upon the results, with the incremental cost per LYG being very sensitive to changes in the accuracy of either test, as explored through sensitivity analyses.

Another key assumption in our model is that the diagnostic accuracy data from the patient population studied in Rondonotti et al (43) are transferable to the patient population we examined in the cost-effectiveness analysis (patients with positive results on their fecal occult blood test who are referred for CT colonography in Ontario). Although this assumption is overshadowed by the uncertainty inherent in the clinical results, it is an important consideration with the future emergence of clinical data and their applicability to patients referred for CT colonography in Ontario.

A number of limitations also exist with the Markov model developed to estimate the additional per-patient cost and outcome for false-negative results. The model does not include de novo cancer development; that is, all cancer cases must progress through the adenoma-carcinoma pathway. There are emerging data that a small percentage of cancers may arise from flat adenomas rather than polyps. It would be expected that radiological methods would miss flat adenomas, decreasing the effectiveness of CT colonography; but the increase in cancer cases would presumably increase the number of false-negative results generated through the use of CT colonography compared with colon capsule endoscopy, thus not affecting the overall result. The costs of colorectal cancer treatment were based on the adapted model and inflated to 2014 $ CAD; however, costs could be expected to increase due to the availability of new treatment options. This may underestimate the cost-effectiveness of colon capsule endoscopy in avoiding false-negatives.

Finally, the model examined the cost-effectiveness of false-negative results for advanced adenomas only, which may underestimate the cost-effectiveness of colon capsule endoscopy; however, the comparative diagnostic accuracy study (43) reports the same sensitivity for adenomas greater than 6 mm in diameter, thus negating any advantage colon capsule endoscopy may have in avoiding false-negatives. The increased risk posed by advanced adenomas in the average age of the patient population modelled (67 years) was also taken into consideration, with development of colorectal cancer being more of a consideration given the time to progress through the entire adenoma-carcinoma pathway. Additionally, as with many models, the extra-colonic findings of CT colonography are not incorporated into the model, and these could provide other benefits to patient outcomes and health.

There are also limitations associated with the 1-year cost of current CT colonography tests in Ontario and the first-year cost if colon capsule endoscopy were introduced to replace all CT colonography procedures or just those in patients with a prior incomplete colonoscopy. We did not include implementation costs or downstream cost offsets, which may fall with the reduction in false-negative results from the base case analysis, resulting in a potential reduction in the budgetary impact over time.

CONCLUSIONS

The cost-effectiveness of colon capsule endoscopy is favourable compared with that of CT colonography, although a degree of uncertainty remains due to the lack of significant difference in the data regarding underlying diagnostic accuracy for the two procedures. The additional cost of unnecessary colonoscopies for patients with false-positive results and additional cost and life-years lost for patients with false-negative results were used to estimate a cost-effectiveness of about $26,750 per LYG for colon capsule endoscopy versus CT colonography. This estimate is highly sensitive to changes in the diagnostic sensitivity of either colon capsule endoscopy or CT colonography and should be interpreted with caution.

The budgetary impact of implementing colon capsule endoscopy would be an additional $2.72 million to replace all CT colonography procedures with colon capsule endoscopy, or an additional $740,000 to replace only CT colonography procedures in patients with an incomplete colonoscopy within 1 year prior to referral.

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APPENDICES

Appendix 1: Literature Search Strategies

1) Database(s): Embase <1996 to 2013 November 27>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

#	Searches	Results
1	exp Colonic Diseases/ use pmez	193040
2	exp Colon Disease/ use emefd	266158
3	exp Colonic Polyps/ use pmez	6235
4	exp Colon Polyp/ use emefd	10368
5	((colon* adj2 (disease* or lesion?)) or ((colorectal or colo-rectal or colon*) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)) or polyp* or (rectal adj2 bleed*)).ti,ab.	586853
6	or/1-5	839734
7	exp Capsule Endoscopy/	6179
8	exp Capsule Endoscopes/ use pmez	340
9	exp Capsule Endoscope/ use emefd	583
10	(((capsule* or videocapsule* or wireless*) adj2 (endoscop* or enteroscop*)) or (colon* adj2 capsule*) or pillcam* or pill cam* or (capsule* adj2 (wireless* or camera* or video*)) or WCE or given imaging).ti,ab,dv.	7922
11	or/7-10	9456
12	(Colon capsule endoscopy or Pillcam colon*).mp.	274
13	(6 and 11) or 12	2828
14	*Economics/ use pmez	10567
15	*Economics, Medical/ use pmez or *Economics, Pharmaceutical/ use pmez	6571
16	exp "Costs and Cost Analysis"/ use pmez	183771
17	exp Models, Economic/ use pmez	10416
18	Markov Chains/ use pmez or Monte Carlo Method/ use pmez	29632
19	Quality-Adjusted Life Years/ use pmez	7362
20	*Economic Aspect/ use emefd	4353
21	Health Economics/ use emefd	15532
22	exp Health Care Cost/ use emefd	168386
23	exp Economic Evaluation/ use emefd	173734
24	exp Pharmacoeconomics/ use emefd	134806
25	(econom* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic* or pharmaco-economic*).ti,ab.	1023531
26	(cost* adj1 (util* or effective* or efficac* or benefit* or consequence* or analy* or minimi* or saving* or breakdown or lowering or estimate* or variable* or allocation or control or illness or sharing or life or lives or affordabl* or instrument* or technolog* or day* or fee or fees or charge or charges)).ti,ab.	222215
27	(decision adj1 (tree* or analy* or model*)).ti,ab.	21906
28	((value or values or valuation) adj2 (money or monetary or life or lives or costs)).ti,ab.	6908

29	(qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.	31259
30	(sensitivity analys*s or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).ti,ab.	47914
31	(unit-cost or unit-costs or markov).ti,ab.	30190
32	or/14-31	1433147
33	13 and 32	207
34	limit 33 to english language	187
35	limit 34 to yr="1998 -Current"	187
36	remove duplicates from 35	156

2) Database(s): Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database (HTA), NHS Economic Evaluation Database (NHSEED)

ID	Search	Hits
#1	MeSH descriptor: [Colonic Diseases] explode all trees	6108
#2	MeSH descriptor: [Colonic Polyps] explode all trees	262
#3	(colon* near/2 (disease* or lesion?)) or ((colorectal or colo-rectal or colon*) near/2 (cancer* or neoplasm* or carcinoma* or tumo?r*)) or polyp* or (rectal near/2 bleed*):ti,ab,kw (Word variations have been searched)	10055
#4	#1 or #2 or #3	11381
#5	MeSH descriptor: [Capsule Endoscopy] explode all trees	96
#6	MeSH descriptor: [Capsule Endoscopes] this term only	21
#7	((capsule* or videocapsule* or wireless*) near/2 (endoscop* or enteroscop*)) or (colon* near/2 capsule*) or pillcam* or "pill cam" * or (capsule* near/2 (wireless* or camera* or video*)) or WCE or "given imaging" (Word variations have been searched)	228
#8	#5 or #6 or #7	228
#9	#4 and #8	24

3 potentially relevant results for each HTA and NHSEED

HEED
capsule* OR videocapsule* OR wireless*
AND
endoscop* OR enteroscop*
OR
colon* AND capsule*
OR
pillcam*
12 potentially relevant results

Appendix 2: Additional Costing

Table A1: Additional Costing for Colonoscopy and Double-Balloon Enteroscopy

Resource Item	Cost, $	References and Comments
Colonoscopy		
Partial assessment	38.05	OSB A418 partial assessment (gastroenterology), consultation and visits, as suggested by expert panel (45)
Direct costs	297.00	OCCI data using CCI code 2.NM.BA-BJ (46)
Professional fee	103.90	OSB Z497/Z499/Z492/Z496/Z494/Z498/Z495/Z491,Z555 and E740 (45)
Average cost	**438.95**	
Double-balloon enteroscopy[a]		
Partial assessment	38.05	OSB A418 (45)
Professional fee	185.15	OSB Z584 small-bowel push enteroscopy; expert panel indicated this fee is also charged for double-balloon enteroscopy (45)
Anaesthesia consultation	106.80	OSB A015 (45)
Anaesthesia (6 basic units and 6 time units)	180.12	OSB (45)
Disposables: overtube and balloon	384.25	Alberta Health (52)
Direct costs	596.00	OCCI data using codes 2.NK.70.BC and 2.NK.70.BD (46)
Average cost	**1,490.37**	

Abbreviations: CCI, Canadian Classification of Health Interventions; OCCI, Ontario Case Costing Initiative; OSB, Ontario Schedule of Benefits.
[a]Cost of double-balloon enteroscopy included to account for its use to retrieve the capsule when it fails to pass through patient's digestive system in the case of capsule retention.

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