Ontario
Health Quality Ontario

Colon Capsule Endoscopy for the Detection of Colorectal Polyps: An Evidence-Based Analysis

HEALTH QUALITY ONTARIO

JULY 2015

Ontario Health Technology Assessment Series; Vol. 15: No. 14, pp. 1–39, July 2015

Suggested Citation

This report should be cited as follows:

Health Quality Ontario. Colon capsule endoscopy for the detection of colorectal polyps: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2015 July;15(14):1–39. Available from: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/eba-colon-capsule-endoscopy.

Indexing

The *Ontario Health Technology Assessment Series* is currently indexed in MEDLINE/PubMed, Excerpta Medica/EMBASE, and the Centre for Reviews and Dissemination database.

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to EvidenceInfo@hqontario.ca.

How to Obtain Issues in the *Ontario Health Technology Assessment Series*

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series.

Conflict of Interest Statement

There are no competing interests or conflicts of interest to declare.

Peer Review

All reports in the *Ontario Health Technology Assessment Series* are subject to external expert peer review. Additionally, Health Quality Ontario posts draft reports and recommendations on its website for public comment prior to publication. For more information, please visit: http://www.hqontario.ca/evidence/evidence-process/evidence-review-process/professional-and-public-engagement-and-consultation.

About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care in Ontario, evaluating the effectiveness of health care technologies and services, providing evidence-based recommendations, reporting to the public on the quality of the health system, and supporting the spread of quality improvement throughout the system.

About the *Ontario Health Technology Assessment Series*

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series,* which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

Disclaimer

This report was prepared by Health Quality Ontario or one of its research partners for the Ontario Health Technology Advisory Committee and was developed from analysis, interpretation, and comparison of scientific research. It also incorporates, when available, Ontario data and information provided by experts and applicants to Health Quality Ontario. It is possible that relevant scientific findings may have been reported since the completion of the review. This report is current to the date of the literature review specified in the methods section, if available. This analysis may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

ABSTRACT

Background

Colorectal cancer, a leading cause of mortality and morbidity in Ontario, can be prevented through early diagnosis and removal of precancerous polyps. Colon capsule endoscopy is a relatively new, minimally invasive test for detecting colorectal polyps.

Objective

The objectives of this analysis were to evaluate the diagnostic accuracy and safety of colon capsule endoscopy for the detection of colorectal polyps among adult patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer, and to compare colon capsule endoscopy with alternative procedures.

Review Methods

A literature search was performed using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid EMBASE, the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published between 2006 and 2014. Data on diagnostic accuracy and safety were abstracted from included studies. Quality of evidence was assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results

The search yielded 2,189 citations. Five studies, all of which evaluated PillCam COLON 2 (PCC2), met the inclusion criteria. The per-patient sensitivity and specificity for detecting colorectal polyps were meta-analyzed. Colon capsule endoscopy, using PCC2, had a pooled sensitivity and specificity of 87% (95% confidence interval [CI] 77%–93%) and 76% (95% CI 60%–87%), respectively, for the detection of a colorectal polyp at least 6 mm in size (GRADE: very low). PCC2 had a pooled sensitivity and specificity of 89% (95% CI 77%–95%) and 91% (95% CI 86%–95%), respectively, for the detection of a colorectal polyp at least 10 mm in size (GRADE: low). One study directly compared PCC2 with computed tomographic (CT) colonography and found no statistically significant difference in accuracy (GRADE: low). Few adverse events were reported with PCC2; 3.9% of patients (95% CI 2.4%–6.5%) experienced adverse effects related to bowel preparation. Capsule retention was the most serious adverse event and occurred in 0.8% of patients (95% CI 0.2%–2.4%) (GRADE: very low).

Conclusions

In adult patients with signs, symptoms, or increased risk of colorectal cancer, there is low-quality evidence that colon capsule endoscopy using the PCC2 device has good sensitivity and specificity for detecting colorectal polyps. Low-quality evidence does not show a difference in accuracy between colon capsule endoscopy and CT colonography. There is very low-quality evidence that PCC2 has a good safety profile with few adverse events; capsule retention is the most serious complication.

PLAIN LANGUAGE SUMMARY

Colon capsule endoscopy is a new procedure that allows doctors to see inside the colon (large intestine) to look for growths, called polyps, that can develop into cancer. In this procedure, the patient swallows a pill fitted with two miniature cameras. As the capsule travels through the patient's gastrointestinal tract, the cameras send pictures of the colon to a data recorder. Doctors then review the images to look for polyps. If polyps are found, they can be investigated further and, if necessary, removed through a different procedure, which can reduce the patient's risk of colorectal cancer.

We looked at the research evidence regarding the accuracy and safety of colon capsule endoscopy. We found that colon capsule endoscopy has good accuracy in detecting colorectal polyps in adults with higher risk of colorectal cancer. We also compared the accuracy of colon capsule endoscopy with computed tomography (CT) scan of the colon (colonography), another diagnostic technique used to detect colorectal polyps. The available evidence did not show a difference between colon capsule endoscopy and CT colonography in terms of their accuracy.

Colon capsule endoscopy was generally safe. Less than 4% of patients experienced an adverse event, such as nausea, and these events were mostly due to the bowel preparation required for the procedure. The most serious complication associated with colon capsule endoscopy was the capsule becoming stuck at a narrowed spot in the digestive tract. This happens rarely, but when it does the patient requires surgery or colonoscopy to remove the capsule.

Compared with conventional colonoscopy, the colon capsule endoscopy procedure may be preferred by patients because it less invasive and uncomfortable and does not require that they be sedated. However, colon capsule endoscopy cannot replace colonoscopy. If polyps are found, a colonoscopy or other procedure may be needed to further investigate and remove precancerous polyps.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CI	Confidence interval
CT	Computed tomographic
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
NaP	Sodium phosphate
PCC	PillCam COLON
PCC2	PillCam COLON 2
SROC	Summary receiver operating characteristic

BACKGROUND

Objectives of Analysis

The objectives of this analysis were to evaluate the diagnostic accuracy and safety of colon capsule endoscopy for the detection of colorectal polyps among adult patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer, and to compare colon capsule endoscopy with alternative procedures.

Clinical Need and Target Population

Description of Disease or Condition

Colorectal cancer is a cancer in the colon or rectum. Most colorectal cancers develop from precancerous polyps. (1) A colorectal polyp, also called an adenoma, is a protrusion of the mucosal surface inside the colon or rectum. These polyps can be benign and asymptomatic, and only dysplastic polyps have the potential to become malignant. The size of the polyp affects both the structure of the tissue and the degree of dysplasia. Larger colorectal polyps are more likely to carry precancerous components and to be dysplastic. An estimated 1% to 5% of adenomatous colorectal polyps will progress to invasive cancer if they are high-grade (severe) dysplastic or larger than 10 mm in diameter. (2) Colorectal polyps larger than 10 mm are considered to be advanced adenoma, while colorectal polyps less than 5 mm generally carry much less risk. (3) Colorectal adenomas have been found in 11% to 40% of patients with average risk of colorectal cancer and at higher rates in the high-risk population. (4, 5) Typically, people at higher risk of colorectal cancer are those with family history of the disease or signs or symptoms of colorectal cancer such as rectal bleeding or abdominal mass. (2)

Since progression from normal mucosa to invasive cancer can take 10 to 15 years, early diagnosis and removal of precancerous polyps is highly effective in preventing the development of colorectal cancer. (6, 7) Canadian clinical guidelines recommend that patients with symptoms and known or suspected colonic disease be promptly examined with colonoscopy and that patients without symptoms undergo regular screening. (3)

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) In 2013, 8,700 Ontarians were estimated to have colorectal cancer, from which 3,350 Ontarians died. (11)

Ontario Context

In Ontario, screening for colorectal cancer is recommended every 2 years using the fecal occult blood test for everyone aged 50 to 74 years without any symptoms of colorectal cancer. For people with increased risk for colorectal cancer or with signs and symptoms of colorectal cancer, colonoscopy is the standard procedure for immediate diagnosis. Many experts believe that colonoscopy is the gold standard for colorectal cancer screening as the procedure allows for the visualization of the entire colon as well as the detection and removal of colorectal polyps during the same procedure. Patients who have an incomplete colonoscopy or contraindications to the procedure are offered virtual colonoscopy, such as computed tomographic (CT)

colonography. Both colonoscopy and CT colonography are covered under the Ontario Health Insurance Plan, although CT colonography is covered only in certain circumstances. (12)

Technology

Description of Colon Capsule Endoscopy

Colon capsule endoscopy is a relatively new diagnostic technology for examining the colon. It is a minimally invasive procedure and does not require sedation.

In 2006, Given Imaging Ltd. launched its first generation of colon capsule endoscopy, PillCam COLON (PCC). The device is a capsule, designed to be ingested by patients, that takes images of the colon as it passes through the gastrointestinal tract. Each side of the capsule is equipped with a camera and an automatic LED (light-emitting diode). Images captured are transmitted to a data recorder that the patient wears externally. The data are compiled and analyzed by RAPID software (Given Imaging Ltd., Yoqneam, Israel), for review by the clinician. A systematic review showed suboptimal sensitivity and specificity of PCC for detection of significant colorectal polyps (a polyp at least 6 mm in diameter or at least three polyps of any size). (13)

A second generation of the device, PillCam COLON 2 (PCC2), was launched in 2010. PCC2 includes new designs in the capsule, data recorder, and software for processing and viewing images. The new capsule is slightly bigger, measuring 11.6 mm × 31.5 mm, than the previous capsule, which measured 11 mm × 31 mm. The angle of view from both cameras has been widened to 172° from 156°, allowing nearly 360° coverage of the colon. The battery of the previous capsule lasts about 10 hours with an inactive period of 1 hour and 45 minutes. This has been redesigned in PCC2 to allow automatic identification of the small bowel. The new capsule works at a slow frame rate of only 14 images per minute until small-bowel images are detected. After reaching the small bowel, the capsule switches into an adaptive frame rate, capturing 35 images per second when in motion and 4 images per second when it is virtually stationary. The improved frame rate increases the number of images taken during rapid colon transit, thus improving colon visualization and further saving battery energy. The new data collector can alert patients undergoing the procedure to continue the bowel preparation according to the protocol. The new RAPID software includes a tool for estimating polyp size and provides a thorough analysis of the mucosal surface and flat lesions. The procedure is complete when the anal verge is visualized or when the capsule is excreted. (14-16)

Bowel Preparation Regimen Required With Colon Capsule Endoscopy

Adequate cleansing of the colon is essential for the visualization of the colonic mucosa. Colon capsule endoscopy requires boosters to help propel the capsule because the colon has only a few spontaneous longitudinal contractions per day. Sodium phosphate (NaP) is the most commonly used booster. One or two boosters of NaP are typically used in addition to polyethylene glycol solution, which is also used in preparation for colonoscopy. The NaP booster accelerates the transit of the PCC2 capsule through the small and large bowels within the operating time of the capsule. The use of NaP may be associated with electrolyte disturbances, acute nephropathy, or kidney failure, and low doses of NaP are generally administered in colon capsule endoscopy in order to reduce the risk of NaP-related adverse events.

Regulatory Status of Colon Capsule Endoscopy

PCC and PCC2 (Given Imaging Ltd., Yoqneam, Israel) are the only colon capsule endoscopy devices licensed by Health Canada and are indicated for visualization of the colon. These devices have the following licence numbers and issue dates:

- PillCam COLON (Given Imaging Ltd., Yoqneam, Israel), Licence No. 73088, Class II. First issued in January 2007. The company stopped marketing the first-generation device as of 2010
- PillCam COLON 2 (Given Imaging Ltd., Yoqneam, Israel), Licence No. 73088, Class II. First issued in November 2009

Scope of Analysis

The European Society of Gastrointestinal Endoscopy has recommended colon capsule endoscopy as an alternative to colonoscopy for colorectal cancer screening in average-risk individuals. (17) In a preliminary scoping of the literature, only one trial evaluating PCC2 in the screening context, which has recruited 884 patients of average risk for colorectal cancer, was identified. The researchers involved with this trial have, to date, reported their data only in an abstract form. (18) Colon capsule endoscopy has also been proposed as an alternative or complementary diagnostic test for patients who have had contraindications to colonoscopy, have had an incomplete colonoscopy, or have refused the procedure. Studies on the use of colon capsule endoscopy in patients with incomplete colonoscopy exist, (19-21) but they do not provide diagnostic accuracy data and instead report on diagnostic yield.

Therefore, based on an initial scoping review and in consultation with clinical experts, we focused on evaluating colon capsule endoscopy in patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer. We specifically focused on whether colon capsule endoscopy can act as a replacement diagnostic test for CT colonography in this patient population.

EVIDENCE-BASED ANALYSIS

Research Questions

- What are the sensitivity and specificity of colon capsule endoscopy, using the PillCam COLON 2 device (PCC2), for the detection of colorectal polyps among adult patients either with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer?
- What are the sensitivity and specificity of colon capsule endoscopy, using PCC2, compared with computed tomographic (CT) colonography for the detection of colorectal polyps among adult patients either with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer?
- What are the adverse events associated with the use of PCC2?

Research Methods

Literature Search

Search Strategy

A literature search was performed on December 12, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews, for studies published from January 1, 2006, to December 12, 2014. (Appendix 1 provides details of the search strategies). Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Publication between January 1, 2006, and December 12, 2014
- Randomized controlled trials, non-randomized clinical trials, systematic reviews, and meta-analyses
- Studies that investigated PCC2 manufactured by Given Imaging Ltd.
- Adult patients (at least 18 years old)
- Patients undergoing colon examination because of signs or symptoms of colorectal cancer or because of an increased risk of colorectal cancer

Exclusion Criteria

- Studies that investigated the first generation of PCC, since it is no longer marketed
- Studies that investigated small-bowel diseases
- Studies that included only patients with low or average risk of colorectal cancer
- Studies that did not use colonoscopy as the reference standard
- Studies that did not report accuracy data

Outcomes of Interest

- Sensitivity (proportion of people with disease who are diagnosed as having the disease)
- Specificity (proportion of people without disease who are diagnosed as not having the disease)
- Adverse events

Statistical Analysis

A bivariate random effects model was used to synthesize the sensitivity and specificity reported in the included studies. (22) In the analysis, the reference tests compared with the PCC2 were assumed to be perfect. The numbers of true-positives, false-positives, false-negatives, and true-negatives were extracted from the published studies, and the 95% confidence intervals were re-calculated. Common measures of heterogeneity such as I^2 index and Cochrane's Q statistics were not used since they are not reliable when the number of studies is small. They are also not designed for quantifying heterogeneity in a bivariate meta-analysis of diagnostic accuracy where sensitivity and specificity are synthesized simultaneously. (23) Instead, the heterogeneity among the included studies was assessed by visually examining the summary receiver operating characteristics (SROC) space and the forest plots. All models were fitted under the general assumption that the reference standard was independent of the index test, conditional on disease status. All analyses were performed using R 3.1.2 software.

Quality of Evidence

The quality of evidence for each included study was examined using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. (24) The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (25) The overall quality was determined to be high, moderate, low, or very low using a step-wise and structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials are high quality. For diagnostic tests, cross-sectional or cohort studies in patients with diagnostic uncertainty and direct comparison of test results with an appropriate reference standard are also considered to be high quality. (26) Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, three main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose-response gradient, and any residual confounding factors. (25) For more detailed information, please refer to the latest series of GRADE articles. (25)

The quality assessment of the evidence is provided in Appendix 2.

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

Results of Evidence-Based Analysis

The database search yielded 2,189 citations published between January 1, 2006, and December 12, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

Five studies met the inclusion criteria. Reference lists of the included studies and clinical trials registries were screened to identify other relevant studies, and no additional citations were identified.

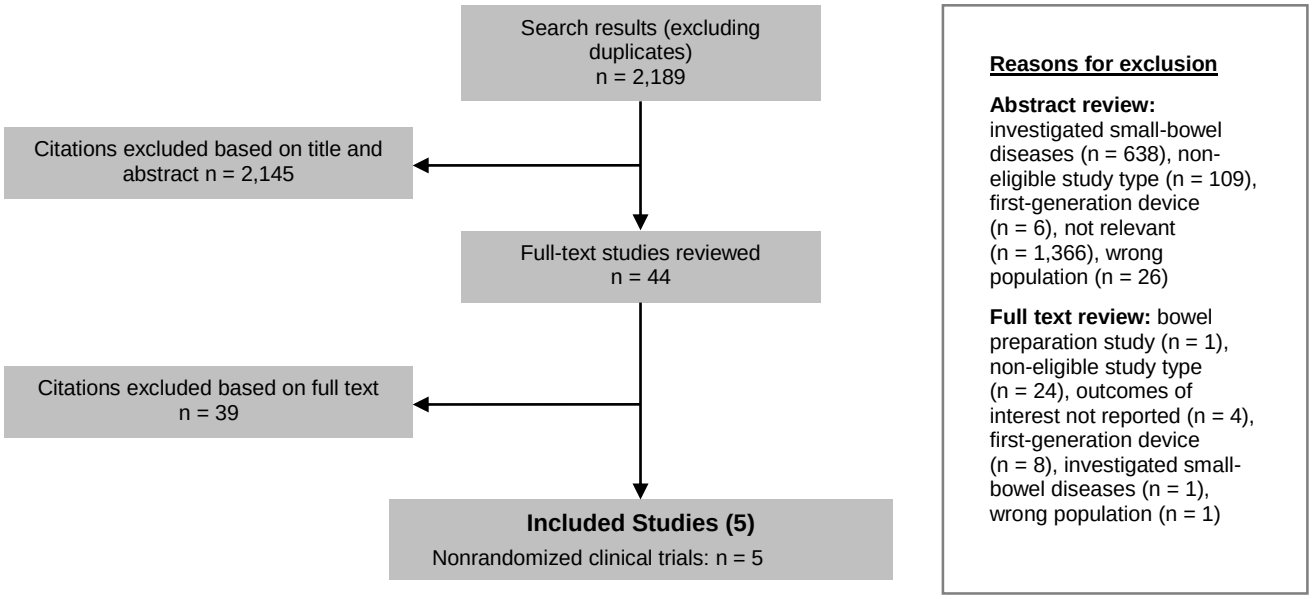


Figure 1: Citation Flow Chart

The five included studies were as follows: one conducted in Israel, reported by Eliakim et al, (27) and four conducted in Europe, reported by Spada et al, (28) Rondonotti et al, (29), Hagel et al (30), and Holleran et al. (31) The target populations of the included studies were mainly adult patients with known or suspected colonic disease, who were scheduled to undergo colonoscopy. On average, patients were 50 to 63 years old. About 54% to 66% were male, and most patients were recruited because they had high risk of colorectal cancer and positive findings from previous tests. The characteristics of the included studies are summarized in Table 1.

Table 1: Characteristics of Included Studies Reporting on the Diagnostic Accuracy of PillCam COLON 2

Study, Country	N (Excluded)[a]	Population	Indications for Colonoscopy[b], n	Index test(s)	Reference Standard	Sponsorship[c]
Eliakim et al, 2009 (27) Israel	104 (6)	Mean age 49.8 y (range 18–57 y); 33 female, 65 male	Patients scheduled to undergo colonoscopy for known or suspected colonic disease: • Personal or family history of CRC, 33 • CRC screening, 31 • Hematochezia or positive FOBT, 21 • Various symptoms (e.g., diarrhea/ constipation, abdominal pain), 17 • Iron-deficiency anemia, 3	PCC2	OC	Given Imaging
Spada et al, 2011 (28) Europe	117 (8)	Mean age 60 y (SD 9 y); 45 female, 72 male	Patients scheduled to undergo colonoscopy for known or suspected colonic disease: • Personal history of polyps/positive findings, 52 • Recent change in bowel habits, 27 • CRC screening, 25 • Rectal bleeding/hematochezia, 23 • Abdominal pain, 18 • Positive FOBT, 7	PCC2	OC	Given Imaging
Rondonotti et al, 2014 (29) Italy	54 (4)	Mean age 59.2 y (SD 5.8 y); 21 female, 29 male	Patients in the national CRC screening program with positive iFOBT for whom colonoscopy was offered, 50	PCC2 and CTC	OC, PCC2, and CTC combined	Fondazione Cariplo
Hagel et al, 2014 (30) Germany	24 (1)	Mean age 51 y (range 24–75 y); 10 female, 14 male	Patients scheduled to undergo colonoscopy for known or suspected colonic disease: • CRC screening – positive family history, 5 • CRC screening – no increased risk, 8 • Polyp surveillance, 7 • Suspected inflammatory bowel disease, 2 • Surveillance colonoscopy in ulcerative colitis, 2	PCC2	OC	Given Imaging
Holleran et al, 2014 (31) Ireland	62	Mean age 62.5 y (SD 5.8 y); 28 female, 34 male	Patients in a pilot CRC screening program with at least 1 positive FOBT result, 62	PCC2	OC	Given Imaging[d]

Abbreviations: CRC, colorectal cancer; CTC, computed tomographic colonography; FOBT, fecal occult blood test; iFOBT, immunochemical fecal occult blood test; OC, optical colonoscopy; PCC2, PillCam COLON 2; SD, standard deviation; y, year.

[a]Patients were excluded from analysis for withdrawal of consent, protocol violation, incomplete preparation, or technology failure

[b]Patients could have more than one reason for being referred to colonoscopy.

[c]Given Imaging is the manufacturer of the PillCam COLON 2 and Fondazione Cariplo is a private philanthropic foundation that funds research projects.

[d]Given Imaging supplied the PCC2 capsules free of charge.

Diagnostic Accuracy of PillCam COLON 2

Colonoscopy was used as the reference standard in four studies. In these studies, patients underwent colon capsule endoscopy using PCC2, followed by colonoscopy after capsule ingestion or on the next day. (27, 28, 30, 31) The colonoscopy was performed by the endoscopist without any knowledge of the results from the PCC2 in all four studies. In the fifth study, the results of the three procedures—colonoscopy, CT colonography, and colon capsule endoscopy using PCC2—were integrated to form the reference standard. (29) Patients underwent the PCC2 first and, after 15 days, they underwent CT colonography in the morning, followed by colonoscopy later that day. The endoscopists performing colonoscopy were blinded to the PCC2 and CT colonography results but were unblinded after inspecting the right colon. If PCC2 or CT colonography found any colorectal polyp that was not reported by the colonoscopy, the endoscopists reached the cecum again and re-inspected the right colon. The same procedure was repeated for the transverse and left colons. The authors defined this procedure as double unblinded colonoscopy and used it as the reference standard.

Three studies reported per-patient sensitivity and specificity of PCC2 for detecting colorectal polyps at least 6 mm and 10 mm in diameter, respectively. (27-29) Hagel et al (30) reported per-patient sensitivity and specificity for detecting a colorectal polyp of any size as well as per-polyp sensitivity and specificity of PCC2 for detecting a colorectal polyp by size or location. Holleran et al (31) reported per-patient sensitivity and specificity of PCC2 for detecting any size colorectal polyps. The polyp-matching algorithms differed between the included studies and are summarized in Table 2.

Table 2: Polyp-Matching Algorithms and Diagnostic Accuracy Outcomes Reported by Included Studies

Study	Reference Standard	Polyp-Matching Algorithm or Rules	Accuracy Data Reported
Eliakim et al, 2009 (27)	OC	A true-positive result was recorded when the colonoscopy found at least a colorectal polyp in corresponding size range and assumed a margin of 50% for size measurement error by PCC2.	• Per patient based on colorectal polyp size: ≥ 6 mm ≥ 10 mm
Spada et al, 2011 (28)	OC	For a colorectal polyp to match, it had to be within 50% of the size of the largest estimate of the two measures and found in same or adjacent segment. True-positive was classified as at least one of colorectal polyps of each size class found in same or adjacent segment.	• Per patient based on colorectal polyp size: ≥ 6 mm ≥ 10 mm • Per patient based on size of neoplastic lesions ≥ 6 mm ≥ 10 mm
Rondonotti et al, 2014 (29)	Integrated results of OC, CTC, and PCC2	When CTC or PCC2 showed at least 1 colorectal polyp 6 mm or larger, confirmed by the RS, the individual was classified as true-positive. If neither the comparative test nor the reference standard identified at least 1 colorectal polyp 6 mm or larger, the individual was classified as true-negative. The individual was categorized as false-positive when the CTC or PCC2 identified at least 1 colorectal polyp 6 mm or larger, not confirmed by the reference standard, and, conversely, as false-negative if the colorectal polyp was missed by the PCC2 or CTC. When 2 or more colorectal polyps were detected in the same person, the largest polyp was considered. The calculation was repeated by setting the colorectal polyp threshold to 10 mm or larger.	• Per patient based on colorectal polyp size with correction for polyp size mismatch: ≥ 6 mm ≥ 10 mm • Per patient based on colorectal polyp size without correction for polyp size mismatch: ≥ 6 mm ≥ 10 mm
Hagel et al, 2014 (30)	OC	Matching of colorectal polyps recorded by PCC2 and by flexible colonoscopy was performed by comparing size, location (right, transverse, and left colon) and morphology. Matching of polyp size was determined if the size measured in OC was within 50% of its reference standard measure at PCC2.	• Per patient based on ≥ 1 colorectal polyp of any size • Per polyp based on colorectal polyp size: < 6 mm 6–9 mm ≥ 10 mm • Per polyp based on colorectal polyp location: Right colon Transverse Left colon
Holleran et al, 2014 (31)	OC	Not described	• Per patient based on any colorectal polyp of any size • Per patient based on significant neoplasia (defined as more than 3 polyps in 1 individual or any polyp > 10 mm)

Abbreviations: CTC, computed tomographic colonography; OC, Optical Colonoscopy; PCC2, PillCam COLON 2.

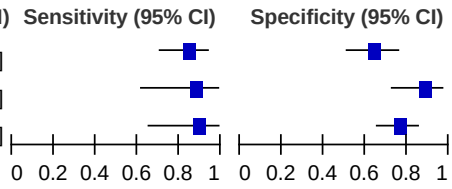
Per-Patient Sensitivity and Specificity

The per-patient sensitivity and specificity for colorectal polyps of varying sizes reported by the included studies (27-31) are summarized in Figure 2.

We used a bivariate model to calculate the pooled per-patient sensitivity and specificity and their 95% confidence regions. This model assumed that the reference standard of each study was perfect. For detecting colorectal polyps 6 mm or greater in diameter, the pooled per-patient sensitivity was 87% (95% CI 77%–93%) and the pooled per-patient specificity was 76% (95% CI 60%–87%). For detecting colorectal polyps 10 mm or greater, the pooled per-patient sensitivity was 89% (95% CI 77%–95%) and the pooled per-patient specificity was 91% (95% CI 86%–95%). The pooled per-patient sensitivity and specificity of PCC2 for the detection of colorectal polyps of any size were 89% (95% CI 66%–97%) and 75% (95% CI 45%–91%), respectively. Figure 3 shows the SROC curves for detecting colorectal polyps of varying sizes. There is a greater degree of heterogeneity among the studies for the detection of polyps 6 mm or greater than among studies for the detection of polyps 10 mm or greater.

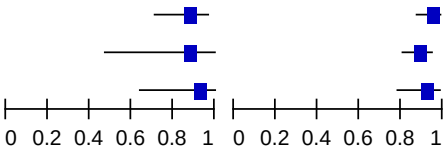
Detection of Colorectal Polyps ≥ 6 mm

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Spada 2011	38	23	7	41	0.84 [0.71, 0.94]	0.64 [0.51, 0.76]
Rondonotti 2014	14	4	2	30	0.88 [0.62, 0.98]	0.88 [0.73, 0.97]
Eliakim 2009	16	19	2	61	0.89 [0.65, 0.99]	0.76 [0.65, 0.85]



Detection of Colorectal Polyps ≥ 10 mm

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Spada 2011	28	4	4	73	0.88 [0.71, 0.96]	0.95 [0.87, 0.99]
Eliakim 2009	7	10	1	80	0.88 [0.47, 1.00]	0.89 [0.81, 0.95]
Rondonotti 2014	12	3	1	34	0.92 [0.64, 1.00]	0.92 [0.78, 0.98]



Detection of Colorectal Polyps of Any Size

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hagel 2014	13	1	3	6	0.81 [0.54, 0.96]	0.86 [0.42, 1.00]
Holleran 2014	34	9	2	17	0.94 [0.81, 0.99]	0.65 [0.44, 0.83]

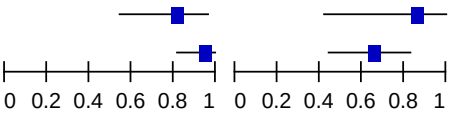


Figure 2: Forest Plots of Accuracy of PillCam COLON 2 in the Detection of Colorectal Polyps of Varying Sizes

Abbreviations: CI, confidence interval; FN, false-negative; FP, false-positive; TN, true-negative; TP, true-positive.

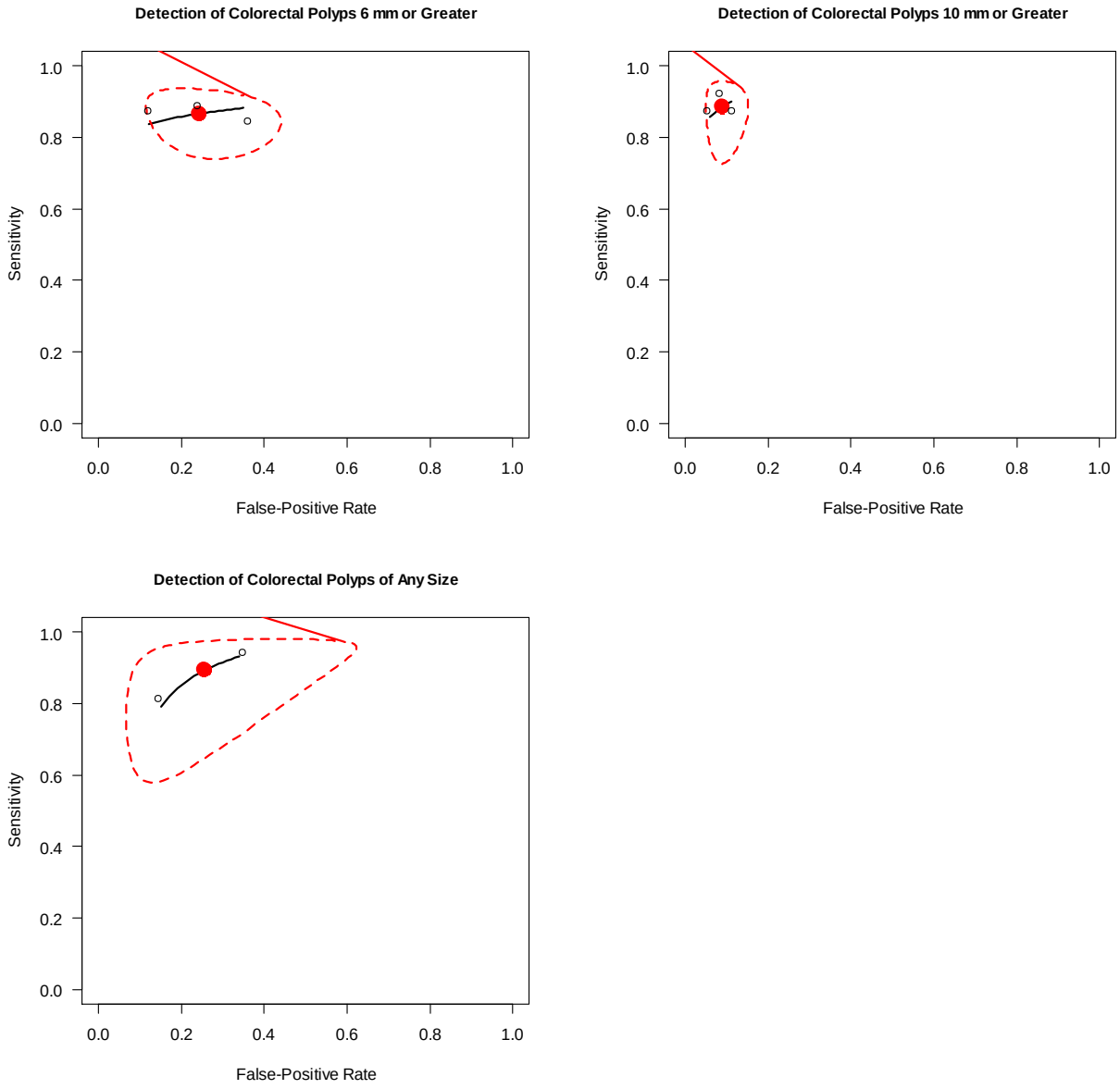


Figure 3: SROC Curves of PillCam COLON 2 in the Detection of Colorectal Polyps of Various Sizes

Abbreviation: SROC, summary receiver operating characteristics.

Note: The solid red dot in the SROC indicates the pooled estimates of sensitivity and specificity. The dashed red line shows the 95% confidence region of the pooled estimate, and represents the uncertainty around the pooled sensitivity and specificity.

Other accuracy outcomes were reported in the included studies but were not included in the pooled analysis. Spada et al (28) reported the per-patient sensitivity and specificity in detection of only neoplastic polyps. For detecting a neoplastic polyp at least 6 mm in size, the per-patient sensitivity and specificity were 90% (95% CI 80%–99%) and 64% (95% CI 52%–76%), respectively. For 10 mm, the per-patient sensitivity and specificity were 93% (95% CI 84%–100%) and 95% (95% CI 90%–100%), respectively. Holleran et al (31) reported a per-patient sensitivity of 89% (no CI reported) and per-patient specificity of 96% (no CI reported) for detecting significant lesions (defined as more than three polyps in one individual or any polyp larger than 10 mm).

Comparative Diagnostic Accuracy of PillCam COLON 2 and Computed Tomographic Colonography

One study presented diagnostic accuracy data of PCC2 directly compared with CT colonography. (29) That study reported the per-patient sensitivity and specificity of CT colonography for detecting polyps 6 mm or greater and 10 mm or greater. Overall, the results showed that PCC2 and CT colonography had comparable accuracy in the detection of colorectal polyps. For detecting any colorectal polyp at least 10 mm in size, PCC2 had a higher sensitivity than CT colonography but the difference was not statistically significant. Table 3 summarizes the comparison between PCC2 and CT colonography.

Table 3: Comparative Accuracy of PillCam COLON 2 and Computed Tomographic Colonography

Outcomes	PCC2, % (95% CI)[a]	CTC, % (95% CI)[a]	*P* Value[b]
Colorectal polyp size ≥ 6 mm			
Sensitivity	88 (62–98)	88 (62–98)	0.99
Specificity	88 (71–96)	85 (67–94)	0.72
Colorectal polyp size ≥ 10 mm			
Sensitivity	93 (64–100)	79 (49–94)	0.26
Specificity	92 (76–98)	92 (76–98)	0.99

Abbreviations: CI, confidence interval; CTC, computed tomographic colonography; PCC2, PillCam COLON 2.
[a]Data from Rondonotti et al, 2014. (29)
[b]*P* value was calculated by testing the null hypothesis that the relative sensitivity and specificity of PCC2 versus CTC was equal to 1. (32)

Safety of PillCam COLON 2

Five studies presented safety data for PCC2 compared with other diagnostic modalities. Eliakim et al (27) reported that, of 104 patients, one could not swallow the PCC2 capsule (1.0%) and one patient had a capsule that was corrupted due to technical failure (1.0%). The authors did not report any adverse event directly related to the capsule procedure. Overall, eight adverse events related to bowel preparation in seven patients (6.7%) were reported: five mild to moderate cases of headache/nausea resolved within 24 hours; two cases of mild vomiting resolved within 48 hours; and one case of urinary retention was rated by the authors as a severe adverse event unrelated to the study. No complications were reported for colonoscopy.

Spada et al (28) reported three cases of capsule retention (2.6%), where the capsule impacted against a tumour and was retrieved by colonoscopy or surgery. One patient (0.9%) was not able to swallow the capsule. There was technical failure of the device for four patients (3.4%): two cases were due to the data recorder and the other two were due to problems with the capsule. In an additional two patients (1.7%), the capsule remained in the cecum during the entire

procedure. A total of seven (6.0%) mild to moderate adverse events were reported: five patients experienced vomiting, nausea, or abdominal pain related to the bowel preparation and two experienced fatigue because of the long procedure. One patient (0.9%) experienced severe abdominal pain during colonoscopy.

Rondonotti et al (29) reported that two of 50 patients undergoing the PCC2 procedure (4.0%) had difficulties in swallowing the capsule. All patients excreted the capsule naturally and no adverse events related to the preparation or examination were reported. Ten of 50 patients (20%) undergoing CT colonography procedures reported mild, self-limiting abdominal pain related to bowel preparation, and two patients (4%) experienced severe pain during the procedure. No complications were reported for colonoscopy.

Hagel et al (30) reported that all 24 patients were able to swallow the capsule. One patient reported headache during preparation for the PCC2 procedure. No other adverse events were reported with PCC2. One colonoscopy examination was terminated in the transverse colon due to unmanageable pain in the patient. No further complications were reported for colonoscopy.

All 62 patients in the study by Holleran and colleagues (31) were able to swallow the colon capsule. No adverse events were reported for PCC2. One participant (2 %) was admitted 24 hours after colonoscopy with a post-polypectomy bleed, which required a blood transfusion, repeat colonoscopy, and clipping of a visible vessel at the polypectomy base.

In summary, 14 of 357 patients (3.9%, 95% CI 2.4%–6.5%) reported mild to moderate adverse events associated with PCC2. The events were primarily related to bowel preparation and included headache, nausea, vomiting, abdominal pain, and fatigue. Four patients (1.1%, 95% CI 0.4%–2.8%) had difficulties in swallowing the capsule. The capsule was retained in three patients (0.8%, 95% CI 0.2%–2.4%), and they required further surgery or colonoscopy to remove the capsule. Five patients (1.4%, 95% CI 0.6%–3.2%) experienced technical failure due to the capsule or the data recorder. The adverse events reported in the included studies are summarized in Table 4.

Table 4: Summary of Adverse Events Reported in Included Studies

Study	Total, n	PillCam COLON 2, n (%)				Colonoscopy, n (%)	CTC, n (%)
		AEs Related to Bowel Preparation	Difficulty in Swallowing Capsule	Capsule Retention	Technical Failure		
Eliakim et al, 2009 (27)	104	7 (6.7)	1 (1.0)	0	1 (1.0)	0	N/A
Spada et al, 2011 (28)	117	7 (6.0)	1 (0.9)	3 (2.6)	4 (3.4)	1 (0.9) Pain	N/A
Rondonotti et al, 2014 (29)	50[a]	0	2 (4.0)	0	0	0	10 (20) Mild pain 2 (4) Severe pain
Hagel et al, 2014 (30)	24	1	0	0	0	1 (4.2) Pain	N/A
Holleran et al, 2014 (31)	62	0	0	0	0	1 (1.6) Bleed[b]	N/A
Total	**357**	**14 (3.9)**	**4 (1.1)**	**3 (0.8)**	**5 (1.4)**	**3 (0.8%)**	**12 (24%)**

Abbreviations: AE, adverse event; CTC, computed tomographic colonography; N/A, not applicable.
[a]Adverse events were not reported for 4 patients excluded from the analysis.
[b]The patient developed a post-polypectomy bleed, which required a blood transfusion, repeat colonoscopy, and clipping of a visible vessel at the polypectomy base.

Discussion

In a patient population at higher risk of colorectal cancer, colon capsule endoscopy using PillCam COLON 2 (PPC2) demonstrated good sensitivity in identifying patients with colorectal polyps. The lower specificity reported by the included studies may be due to polyp size mismatching between colon capsule endoscopy and colonoscopy (generating false-positives). Alternatively, it may be the case that polyps were missed by colonoscopy, in which case the specificity would be greater than we report. We identified heterogeneity in the sensitivity and specificity values reported, which may have been due to differences in the level of bowel preparation among the included studies; adequate bowel preparation is essential for polyp detection with colon capsule endoscopy.

One study directly compared colon capsule endoscopy with CT colonography. There was no statistically significant difference in sensitivity between colon capsule endoscopy and CT colonography, in identifying polyps 10 mm or greater in diameter. Colon capsule endoscopy had the same specificity as CT colonography in identifying both larger and smaller polyps and the same sensitivity in identifying smaller polyps (≥ 6 mm). The two diagnostic modalities have similar accuracy.

In general, colon capsule endoscopy was well tolerated by patients in the included studies. The most common adverse events were headache, nausea, and vomiting, which were primarily related to the bowel preparation. Capsule retention was the most serious complication and occurred in fewer than one in 100 patients.

The role of colon capsule endoscopy in patients who have signs, symptoms, or increased risk of colorectal cancer remains uncertain. Some authors have suggested that, due to the low number of false-positive results, the use of colon capsule endoscopy can decrease the number of patients exposed to unnecessary colonoscopy. (31) However, a high level of false-negative results may result in late diagnosis of colorectal cancer. This may be of particular concern in the patient population included in this review (i.e., people at higher risk of colorectal cancer), who will have a higher pretest probability of colorectal cancer.

Others have suggested that colon capsule endoscopy be used for patients with incomplete colonoscopy as capsule endoscopy can identify significant findings and guide further endoscopic investigations, and patients largely accept the procedure. (21) However, research from studies in patients with incomplete colonoscopies is limited as diagnostic accuracy is not reported due to the lack of a reference standard.

Limitations

Interpretation of the results of this review is limited by several factors.

First, the accuracy of colonoscopy, which was used as the reference standard or as component of the reference standard in all the included studies, may be imperfect. It was reported that the miss rate for colorectal polyps of any size by colonoscopy was 22% (2% for size ≥ 10 mm, 13% for size 5–10 mm, and 26% for size 1–5 mm). (33) Colorectal polyps missed by colonoscopy potentially affect the estimated accuracy of PCC2.

Second, the colorectal polyp size was calculated by software specifically designed for PCC2. The accuracy of this software in estimating the size of colorectal polyps had not been previously validated.

Finally, the patient populations of the included studies were adults who agreed to undergo two, and even three, procedures (colon capsule endoscopy, colonoscopy, and CT colonography). These patients may not reflect those in real-world settings, and therefore the results of the analyses might not be generalizable to a wider population.

CONCLUSIONS

In patients with signs or symptoms of colorectal cancer or with increased risk of colorectal cancer, colon capsule endoscopy, using the PillCam COLON 2 device, has:

- 87% sensitivity and 76% specificity for detecting a colorectal polyp at least 6 mm in size (GRADE: very low)
- 89% sensitivity and 91% specificity for detecting a colorectal polyp at least 10 mm in size (GRADE: low)
- 89% sensitivity and 75% specificity for detecting a colorectal polyp of any size (GRADE: very low)
- No statistically significant difference in sensitivity or specificity compared with that of computed tomographic colonography (GRADE: low)
- A good safety profile with few adverse events (GRADE: very low), although there is a risk of capsule retention, which may require surgery or colonoscopy to remove the capsule

Colon capsule endoscopy enables visualization of the entire colon and has good accuracy as a diagnostic test. However, the technology lacks the capability to support biopsy or removal of polyps, which is possible with conventional colonoscopy.

EXISTING GUIDELINES RELEVANT TO COLON CAPSULE ENDOSCOPY

Thirteen guidelines on screening for colorectal cancer were identified, of which eight made no reference to colon capsule endoscopy. Five guidelines did refer to colon capsule endoscopy but stated that the use of the technology in colorectal cancer screening is unclear due to insufficient evidence. The recommendations on colon capsule endoscopy are summarized in Table 5. A protocol for a revised guideline on colorectal cancer screening has recently been published, but colon capsule endoscopy was specifically excluded from the assessment of screening tests. (34)

Table 5: Existing Guidelines for the Use of Colon Capsule Endoscopy in Screening for Colorectal Cancer

Organization, Year	Recommendations	Strength of Evidence	Strength of Recommendation
Asia Pacific Working Group on Colorectal Cancer, 2015 (35)	"A role for capsule endoscopy in colorectal cancer screening is not defined. It may be used in cases when total colonoscopy is not possible."	II-2[a]	B[b]
British Columbia Medical Services Commission, 2013 (36)	No mention of the use of CCE in the screening for CRC	N/A	N/A
American College of Physicians, 2012 (37)	No mention of the use of CCE in the screening for CRC	N/A	N/A
Korean Society of Gastrointestinal Endoscopy, 2012 (38)	No mention of the use of CCE in the screening for CRC	N/A	N/A
Cancer Council Australia, 2011 (39)	"While there is interest in its potential for imaging the large bowel, the place for video-capsule colonoscopy is still uncertain."	NR	NR
Scottish Intercollegiate Guidelines Network, 2011 (40)	"Colon capsule endoscopy is a new and relatively non-invasive modality for examining the colon. At present there is insufficient evidence to determine its role in the diagnosis of colorectal cancer."	2++[c]	NR
British Society of Gastroenterology and the Association of Coloproctology of Great Britain and Ireland, 2010 (41)	No mention of the use of CCE in the screening for CRC	N/A	N/A
Canadian Association of Gastroenterology, 2010 (42)	Colon capsule endoscopy is mentioned as a possible alternative to computed tomographic colonoscopy in select patients; however, no recommendation is made because "contemporary comparative studies are limited."	N/A	N/A
European Commission, 2010 (43)	"There currently is no evidence on the effect of new screening tests under evaluation on CRC incidence and mortality. New screening technologies such as … capsule endoscopy should therefore not be used for screening the average-risk population."	IV[d]	D[e]
National Comprehensive Cancer Network, 2010 (44)	No mention of the use of CCE in the screening for CRC	N/A	N/A

Organization, Year	Recommendations	Strength of Evidence	Strength of Recommendation
American College of Gastroenterology, 2008 (45)	No mention of the use of CCE in the screening for CRC	N/A	N/A
U.S. Multi-Society Task Force on Colorectal Cancer, 2008 (46)	No mention of the use of CCE in the screening for CRC	N/A	N/A
U.S. Preventive Services Task Force, 2008 (47)	No mention of the use of CCE in the screening for CRC	N/A	N/A

Abbreviations: CCE, colon capsule endoscopy; CRC, colorectal cancer; N/A, not applicable; NR, not reported.
[a]Evidence obtained from well-designed cohort or case-control study.
[b]There is fair evidence to support the statement.
[c]High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
[d]Retrospective case-control studies or systematic reviews of case-control studies, time-series analyses.
[e]Intervention not recommended.

We also identified one guideline written specifically to provide general recommendations on the potential implementation of colon capsule endoscopy. (17) The guideline states that colon capsule endoscopy is feasible and safe and appears to be accurate when used in average-risk patients. The recommendations are summarized in Table 6.

Table 6: Existing Guideline for the Potential Implementation of Colon Capsule Endoscopy

Organization, Year	Recommendations	Strength of Evidence	Strength of Recommendation
European Society of Gastrointestinal Endoscopy, 2012. (17)	"CCE is feasible and safe and appears to be accurate when used in average-risk individuals."	2++[a]	D[b]
	"There is a lack of specific studies based in the setting of screening. CCE screening may be cost-effective if it increases screening uptake compared with colonoscopy."	4[c]	D[b]
	"Patients at high risk for CRC, because of alarm symptoms or signs, or a family or personal history of CRC, are at increased risk of advanced colorectal neoplasia and cancer. These patients should be referred for colonoscopy. However, in patients for whom colonoscopy is inappropriate or not possible, the use of CCE could be discussed with the patient."	4[c]	D[b]
	"CCE is a feasible and safe tool for visualization of the colonic mucosa in patients with incomplete colonoscopy and without stenosis."	3[d]	D[b]
	"Randomized studies comparing CCE with radiological imaging or conventional endoscopic modalities are needed to confirm the efficacy of CCE in this setting and to better define the patients for whom CCE is most suitable."	4[c]	D[b]
	"Contraindications for CCE are similar to those for small-bowel capsule endoscopy. The use of sodium phosphate as a booster should be avoided in patients at increased risk of sodium phosphate toxicity. Other kinds of booster preparations are under investigation and may be considered in patients at increased risk of sodium phosphate toxicity."	4[c]	D[b]

Abbreviations: CCE, colon capsule endoscopy.
[a]High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
[b]Evidence level 2− or 3 or 4; or extrapolated evidence from studies rated as 2+.
[c]Nonanalytic studies, e. g., case reports, case series.
[d]Expert opinion.

ACKNOWLEDGEMENTS

Editorial Staff
Amy Zierler, BA

Medical Information Services
Corinne Holubowich, BEd, MLIS

Experts Consulted on Colon Capsule Endoscopy and Colonoscopy

Experts	Representation	Affiliation
Dr. Michael Gould	Gastroenterologist Medical Director and President	Cancer Care Ontario Clinical Lead Vaughan Endoscopy Clinic
Dr. Samir Grover	Gastroenterologist	St. Michael's Hospital
Dr. Elaine Yong	Gastroenterologist	Sunnybrook Health Sciences Centre

APPENDICES

Appendix 1: Literature Search Strategies

Search date: December 12, 2014
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, EMBASE, All EBM Databases (see below)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 2014>, EBM Reviews - ACP Journal Club <1991 to November 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <November 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <4th Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2014>, EMBASE <1980 to 2014 Week 49>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

#	Searches	Results
1	exp Colonic Diseases/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	204786
2	exp colon disease/ use emez	370552
3	exp Colonic Polyps/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	6864
4	exp colon polyp/ use emez	14416
5	((colon* adj2 disease*) or ((colorectal or colonic) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)) or polyp* or (rectal adj2 bleed*)).ti,ab.	644171
6	or/1-5	1027936
7	exp Capsule Endoscopy/	7104
8	exp Capsule Endoscopes/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	438
9	exp capsule endoscope/ use emez	685
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.	19371
11	or/7-10	21162
12	6 and 11	3292
13	limit 12 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	2951
14	limit 13 to yr="2006 -Current" [Limit not valid in DARE; records were retained]	2626
15	remove duplicates from 14	2189

Appendix 2: Evidence Quality Assessment

Table A1: GRADE Diagnostic Accuracy Evidence Profile for PillCam COLON 2 for Detection of Colorectal Polyps

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Per-patient accuracy of PillCam COLON 2 for detection of colorectal polyps ≥ 6 mm							
3 (diagnostic accuracy studies)	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕ Very low
Per-patient accuracy of PillCam COLON 2 for detection of colorectal polyps ≥ 10 mm							
3 (diagnostic accuracy studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕⊕ Low
Per-patient accuracy of PillCam COLON 2 for detection of colorectal polyps of any size							
2 (diagnostic accuracy studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]In 4 of 5 studies reporting any diagnostic accuracy data, the patients were not selected randomly or consecutively; in 1 study the reference standard integrated results from the two index tests; in 4 of 5 studies not all patients were included in the analysis.

[b]Inconsistency in the range of specificities reported that could not be explained by the quality of the studies or included population.

[c]Small sample size.

Table A2: GRADE Diagnostic Accuracy Evidence Profile: PillCam COLON 2 Compared With Computed Tomographic Colonography

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Per-patient accuracy of PillCam COLON 2 versus computed tomographic colonography for detection of colorectal polyps ≥ 6 mm							
1 (diagnostic accuracy study)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low
Per-patient accuracy of PillCam COLON 2 versus computed tomographic colonography for detection of colorectal polyps ≥ 10 mm							
1 (diagnostic accuracy study)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕⊕ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Patients were not selected randomly or consecutively; the reference standard integrated results from the two index tests; and not all patients were included in the analysis.

[b]Small sample size.

Table A3: GRADE Evidence Profile for PillCam COLON 2: Adverse Events

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Adverse events							
5 (diagnostic accuracy studies)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⊕ Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Poor reporting of adverse events (lack of detail on definition of events, monitoring of events).

[b]Small sample size.

Table A4: Risk of Bias for Studies of PillCam COLON 2 (QUADAS-2)

Author, Year	Risk of Bias			
	Patient Selection	Index Test	Reference Standard[a]	Flow and Timing
Eliakim et al, 2009 (27)	High[b]	Low	Low	High[c]
Spada et al, 2011 (28)	High[b]	Low	Low	High[c]
Rondonotti et al, 2014 (29)	High[b]	Low	High[d]	High[c]
Hagel et al, 2014 (30)	High[b]	Low	Low	High[c]
Holleran et al, 2014 (31)	Low	Low	Low	Low

Abbreviations: QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies.
[a]The accuracy of the reference standard was imperfect but the associated risk of bias was assumed to likely be low.
[b]Patients were not selected randomly or consecutively.
[c]Not all patients were included in the analysis.
[d]The reference standard integrated results from the two index tests (computed tomographic colonography and PillCam COLON 2) and colonoscopy.

REFERENCES

(1) Bond JH. Colon polyps and cancer. Endoscopy. 2003;35(1):27-35.

(2) Cancer Care Ontario. Clinical reference colorectal cancer screening [Internet]. Toronto: Cancer Care Ontario; 2008 [cited 2014 December 8]. Available from: http://health.gov.on.ca/en/pro/programs/coloncancercheck/docs/ccc_refcard_20080606.pdf

(3) Leddin D, Hunt R, Champion M, Cockeram A, Flook N, Gould 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.

(4) Betes Ibanez M, Munoz-Navas MA, Duque JM, Angos R, Macias E, Subtil JC, et al. Diagnostic value of distal colonic polyps for prediction of advanced proximal neoplasia in an average-risk population undergoing screening colonoscopy. Gastrointest Endosc. 2004;59(6):634-41.

(5) Silva AC, Wellnitz CV, Hara AK. Three-dimensional virtual dissection at CT colonography: unraveling the colon to search for lesions. Radiographics. 2006;26(6):1669-86.

(6) Atkin WS, Edwards R, Kralj-Hans I, Wooldrage K, Hart AR, Northover JM, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet. 2010;375(9726):1624-33.

(7) Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329(27):1977-81.

(8) McLeod RS, Canadian Task Force on Preventive Health Care. Screening strategies for colorectal cancer: a systematic review of the evidence. Can J Gastroenterol. 2001;15(10):647-60.

(9) Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.

(10) Canadian Cancer Society. Colorectal cancer statistics [Internet]. 2014 [cited 2014 December 8]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/colorectal/statistics/?region=on

(11) Cancer Care Ontario. Colorectal cancer screening [Internet]. 2013 [cited 2014 December 8]. Available from: https://www.cancercare.on.ca/pcs/screening/coloscreening

(12) Ministry of Health and Long-Term Care. Schedule of benefits for physician services under the Health Insurance Act [Internet]. 2014 [cited 2015 January 18]. Available from: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/d_radiol.pdf

(13) Spada C, Hassan C, Marmo R, Petruzziello L, Riccioni ME, Zullo A, et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clin Gastroenterol Hepatol. 2010;8(6):516-22.

(14) Riccioni ME, Urgesi R, Cianci R, Bizzotto A, Spada C, Costamagna G. Colon capsule endoscopy: advantages, limitations and expectations. Which novelties? World J Gastrointest Endosc. 2012;4(4):99-107.

(15) Spada C, Hassan C, Sturniolo GC, Marmo R, Riccioni ME, de Franchis R, et al. Literature review and recommendations for clinical application of Colon Capsule Endoscopy. Dig Liver Dis. 2011;43(4):251-8.

(16) Sieg A. Capsule endoscopy compared with conventional colonoscopy for detection of colorectal neoplasms. World J Gastrointest Endosc. 2011;3(5):81-5.

(17) Spada C, Hassan C, Galmiche JP, Neuhaus H, Dumonceau JM, Adler S, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2012;44(5):527-36.

(18) Rex DK, Adler SN, Aisenberg J, Burch WC, Carretero C, Chowers Y, et al. Accuracy of PillCam COLON 2 for detecting subjects with adenomas ≥ 6 mm. Gastrointest Endosc. 2013;77:AB29.

(19) Pioche M, de Leusse A, Filoche B, Dalbies PA, Adenis Lamarre P, Jacob P, et al. Prospective multicenter evaluation of colon capsule examination indicated by colonoscopy failure or anesthesia contraindication. Endoscopy. 2012;44(10):911-6.

(20) Negreanu L, Babiuc R, Bengus A, Sadagurschi R. PillCam COLON 2 capsule in patients unable or unwilling to undergo colonoscopy. World J Gastrointest Endosc. 2013;5(11):559-67.

(21) Triantafyllou K, Viazis N, Tsibouris P, Zacharakis G, Kalantzis C, Karamanolis DG, et al. Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further workup in clinical practice. Gastrointest Endosc. 2014;79(2):307-16.

(22) Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005;58(10):982-90.

(23) Zhou Y, Dendukuri N. Statistics for quantifying heterogeneity in univariate and bivariate meta-analyses of binary data: the case of meta-analyses of diagnostic accuracy. Stat Med. 2014;33(16):2701-17.

(24) Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.

(25) Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380-2.

(26) Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336(7653):1106-10.

(27) Eliakim R, Yassin K, Niv Y, Metzger Y, Lachter J, Gal E, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy. 2009;41(12):1026-31.

(28) Spada C, Hassan C, Munoz-Navas M, Neuhaus H, Deviere J, Fockens P, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc. 2011;74(3):581-9 e1.

(29) Rondonotti E, Borghi C, Mandelli G, Radaelli F, Paggi S, Amato A, et al. Accuracy of capsule colonoscopy and computed tomographic colonography in individuals with positive results from the fecal occult blood test. Clin Gastroenterol Hepatol. 2014;12(8):1303-10.

(30) Hagel AF, Gabele E, Raithel M, Hagel WH, Albrecht H, de Rossi TM, et al. Colon capsule endoscopy: detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies. Can J Gastroenterol Hepatol. 2014;28(2):77-82.

(31) Holleran G, Leen R, O'Morain C, McNamara D. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy. 2014;46(6):473-8.

(32) Pepe MS. The statistical evaluation of medical tests for classification and prediction. New York: Oxford University Press; 2004. Chapter 3, Comparing binary tests and regression analysis; p. 35-65.

(33) van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101(2):343-50.

(34) U.S. Preventive Services Task Force. Final research plan: colorectal cancer: screening [Internet]. 2014 [cited 2014 December 29]. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/ResearchPlanFinal/colorectal-cancer-screening2

(35) Sung JJ, Ng SC, Chan FK, Chiu HM, Kim HS, Matsuda T, et al. An updated Asia Pacific Consensus Recommendations on colorectal cancer screening. Gut. 2015;64(1):121-32.

(36) Guidelines and Protocols Advisory Committee. Colorectal screening for cancer prevention in asymptomatic patients [Internet]. Victoria (BC): British Columbia Medical Services Commission; 2013 [cited 2014 December 29]. Available from: http://www.bcguidelines.ca/pdf/colorectal_screening.pdf

(37) Qaseem A, Denberg TD, Hopkins RH, Jr., Humphrey LL, Levine J, Sweet DE, et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med. 2012;156(5):378-86.

(38) Lee BI, Hong SP, Kim SE, Kim SH, Kim HS, Hong SN, et al. Korean guidelines for colorectal cancer screening and polyp detection. Clin Endosc. 2012;45(1):25-43.

(39) Cancer Council Australia. Clinical practice guidelines for surveillance colonoscopy — in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease [Internet]. Sydney: Cancer Council Australia; 2011 [cited 2014 December 29]. Available from: http://wiki.cancer.org.au/australiawiki/images/f/fe/Colonoscopy_Surveillance_Guidelines_FINAL_version_approved_Dec2011-boomarked2.pdf

(40) Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of colorectal cancer: a national clinical guideline [Internet]. Edinburgh: SIGN; 2011 [cited 2014 December 29]. Available from: http://www.sign.ac.uk/pdf/sign126.pdf

(41) Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59(5):666-89.

(42) Leddin DJ, Enns R, Hilsden R, Plourde V, Rabeneck L, Sadowski DC, et al. Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. Can J Gastroenterol. 2010;24(12):705-14.

(43) European Comission. European guidelines for quality assurance in colorectal cancer screening and diagnosis [Internet]. Luxembourg: Publications Office of the European Union; 2010 [cited 2014 December 30]. Available from: http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=ND3210390

(44) Burt RW, Barthel JS, Dunn KB, David DS, Drelichman E, Ford JM, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. J Natl Compr Canc Netw. 2010;8(1):8-61.

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

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

(47) U.S. Preventive Services Task Force. Final recommendation statement: colorectal cancer: screening [Internet]. 2008 [cited 2014 December 29]. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4606-6252-6 (PDF)