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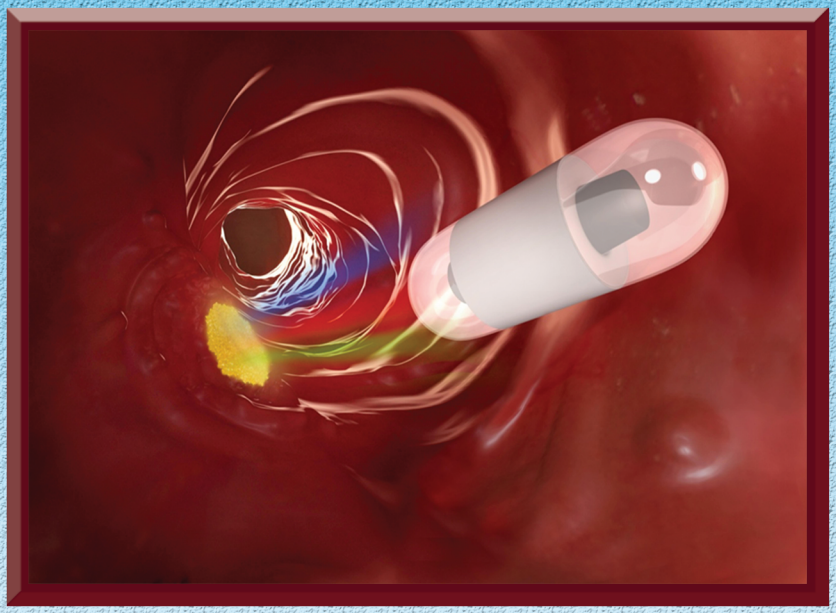
HEALTH TECHNOLOGY ASSESSMENT REPORT

MINISTRY OF HEALTH MALAYSIA

CAPSULE ENDOSCOPY FOR COLORECTAL CANCER SCREENING



MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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CAPSULE ENDOSCOPY FOR COLORECTAL CANCER SCREENING

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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EXECUTIVE SUMMARY

Background

Colorectal cancer (CRC) develops slowly from a growth of tissue or polyp on the inner lining of the colon or rectum over a period of 10 to 20 years. It is a largely preventable disease which requires community participation in the prevention process, such as life style modification and proper screening, early detection and removal of adenomatous polyps (precancerous polyps). The latest, updated Asia Pacific Consensus Recommendations for Colorectal Cancer Screening specifies the age range for CRC screening as 50 to 75 years. Low risk individuals are asymptomatic individuals who are below the age of 50 years while average risk individuals are asymptomatic individuals who aged 50 years and above. Individuals at increased risk of CRC include individuals with 1) history of adenomatous polyps or CRC; 2) family history of either CRC or colorectal adenomas diagnosed in a first degree relative 3) history of inflammatory bowel disease of significant duration; or 4) known or suspected presence of one of two hereditary syndromes (Lynch syndrome or familial adenomatous polyposis). Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008. According to the latest report of the National Cancer Registry (NCR) in Malaysia 2007, colorectal cancer (CRC) is the commonest cancer among men and the second most common cancer among women. A total of 2,246 cases were diagnosed in 2007 and reported to NCR, representing 12.3 % of all cancer cases reported. The incidence of colorectal cancer in 2007 was slightly higher among males with age-standardised rate (ASR) of 13.4 per 100,000 population compared to females (ASR 10.2 per 100,000 population). The incidence was highest among Chinese where the ASR for males and females were 19.4 and 14.6 per 100,000 populations, respectively.

Technical features

The first generation colon capsule endoscopy (CCE-1) which was produced in Israel, uses a small, wireless camera contained in an easy-to-swallow and disposable capsule specifically designed to visualize the colon. The envelope of the capsule is made of biocompatible materials, sealed with biocompatible adhesives. The capsule measures 31 by 11 mm and has two imagers that enable it to acquire video images from both ends. The angle of view from each imager is 156°. It has a total operating time of 10 hours. At the beginning of the examination, CCE is turned on and transmits images for 3 min before it enters a “sleep” mode for 1 hour and 45 min to save battery energy. After this time, it automatically switches on and reactivates in the terminal ileum, allowing a complete colonic exploration.

The second generation colon capsule endoscopy (CCE-2) is similar to CCE-1 except it consists of a slightly bigger, ingestible video capsule. The CCE-2 has two imagers with a much wider angle of view that has been increased to 172 degrees per imager, allowing nearly 360 degrees coverage of the colon. The most unique feature of the CCE-2 is its adaptive frame rate (AFR). This new technology allows the CCE-2 to capture 35 images per second when in motion and 4 images per second when virtually stationary. CCE-2 has been provided with a new portable wireless data recorder able to automatically identify when the CCE enters the small bowel. It also has a user-friendly interface, sending active, customised reminders to the patient, mainly in relation to the different laxative booster intake after capsule ingestion and when the procedure ended.

Policy question

Should capsule endoscopy be used to screen adult population for colorectal cancer?

Objectives

1. To determine the diagnostic accuracy of capsule endoscopy for CRC screening in adult population compared with conventional colonoscopy.
2. To assess the safety of capsule endoscopy compared with conventional colonoscopy in CRC screening.
3. To determine the effectiveness of CRC screening using capsule endoscopy compared with conventional colonoscopy, with regards to patient outcomes such as detection rate, cancer mortality rate, survival rate, quality of life and quality adjusted life years (QALY) gained.
4. To determine the economic evaluation of using capsule endoscopy compared with conventional colonoscopy for CRC screening.
5. To assess the ethical, legal, and organizational aspects related to CRC screening using capsule endoscopy.

Methods

Electronic databases such as MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning database, INAHTA database, HTA database and FDA database were searched. No limits were applied to the search. Additional articles were identified from bibliographies of retrieved articles and hand-searching of journals. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results and conclusion

A total of 1435 titles were identified through the Ovid interface and PubMed. The inclusion criteria included systematic review studies, randomised controlled trials (RCT), diagnostic accuracy studies, observational and economic evaluation studies on capsule endoscopy. The search was limited to adults aged 18 years and above. The exclusion criteria included animal study, narrative review and laboratory study as well as studies on hereditary colorectal cancer. Finally, eighteen full text articles were included in the review which comprised of three meta-analyses, one cost-effectiveness analysis and 14 observational studies.

Diagnostic accuracy and effectiveness

In the first generation capsule endoscopy (CCE-1), there was fair to good level of evidence that showed its accuracy in detecting polyps in patients with average risk (asymptomatic patients aged 50 years and above) and increased risk of CRC (individuals with personal and family history of adenomatous polyps or CRC, history of inflammatory bowel disease or those diagnosed with hereditary non-polyposis colon cancer or familial adenomatous polyposis). The sensitivity and specificity ranged from 68 - 84% and 62 - 92%, respectively. Its positive predictive value (PPV) ranged from 20 – 77% and negative predictive value (NPV) ranged from 71 - 93%. The diagnostic yield of the CCE-1 in detecting CRC ranged from 27 – 76%.

In second generation capsule endoscopy (CCE-2), there was also fair to good level of evidence that suggested its accuracy in detecting polyps and CRC among the average and increased risk patients. For the detection of polyps, CCE-2 showed sensitivity and specificity of 84 – 90% and 64 – 76%, respectively while its detection rate for CRC ranged from 90% to 93%.

The accuracy of CCE-1 was found to be suboptimal as compared to colonoscopy. There were wide variations in the sensitivity, specificity, positive predictive value and negative predictive value of CCE-1 reported in the studies. The sensitivity of CCE-2 was found to be comparable to the sensitivity of colonoscopy although the specificity was slightly low. There was no retrievable evidence on mortality rate, survival rate and quality of life related to screening CRC using capsule endoscopy in the general population.

Safety

There was fair level of evidence to show that both CCE-1 and CCE-2 were safe to be used in the screening for colorectal cancer among the average and increased risk patients. Most of the adverse events were mild and related to bowel preparation. Both types of capsule endoscopy claimed to have received CE mark, with CCE-2 received US FDA approval to be used in cases of failed or incomplete colonoscopy.

Cost effectiveness

There was limited evidence on cost-effectiveness of CCE-1 in screening for CRC. In the Markov model, a hypothetical population of 100,000 individuals aged 50 years and over who underwent a 10 yearly screening procedure, the incremental cost–effectiveness (compared with no screening) of colonoscopy and capsule endoscopy was $16,165 and $29,244 per life–year saved, respectively. With 30% increase in compliance to screening, CCE-1 became more cost-effective than colonoscopy. However, there was no retrievable evidence on economic evaluation conducted on CCE-2.

The cost per capsule was reported to be around RM 1,688.25 (USD 500; 1 USD = RM 3.37).

Organizational

Level of accuracy of capsule endoscopy depends on the adequacy of bowel preparation and the experience of the readers. Spada et al. and Van Gossum et al. found that sensitivity of CCE was significantly higher in the patients with good or excellent cleanliness as compared with the patients with poor or fair cleanliness.Sidhu et al. found that the interpretation of CCE images was largely dependent on the expertise and experience of the gastroenterologist. Jang et al. also showed that the inter-observer differences were greatest for subtle lesions which were often missed by trainees and that experience with conventional endoscopy is important in reviewing CCE findings. Hence, proper and continuous training of staff is essential especially in reading and interpreting CCE images.

Good acceptability and higher uptake of capsule endoscopy was found among average and increased risk of CRC patients. Groth et al. found that offering capsule endoscopy led to a fourfold increase of screening uptake compared to standard colonoscopy while Pilz et al. found that patients preferred capsule endoscopy to colonoscopy. Capsule endoscopy was also found to be feasible and easily performed as an out-of-clinic procedure according to a study done by Adler et al.

Triantafyllou et. al and Pioche et al. found that capsule endoscopy performed after colonoscopy failure or in those contraindicated for colonoscopy is feasible and safe. Hence, in individuals at high risk and contraindicated for conventional colonoscopy, or those who are unwilling to undergo colonoscopy, capsule endoscopy could provide an alternative to conventional colonoscopy.

Recommendation

The accuracy of CCE-1 was found to be suboptimal as compared to colonoscopy. There were wide variations in the sensitivity, specificity, positive predictive value and negative predictive value of CCE-1 reported in the studies. The sensitivity of CCE-2 was found to be comparable to the sensitivity of colonoscopy although the specificity was slightly low. There was no retrievable evidence on mortality rate, survival rate and quality of life related to screening CRC using capsule endoscopy in the general population.

Based on this review, CCE-2 may be considered as a diagnostic tool to identify colonic polyps or CRC among patients with average or increased risk of CRC, particularly among those who are unwilling to undergo colonoscopy, have contraindication for colonoscopy and have history of incomplete colonoscopy.

However, for general population screening for CRC, capsule endoscopy cannot be recommended yet until further quality evidence is available.

TABLE OF CONTENTS

ABBREVIATIONS

HTA	Health Technology Assessment
CRC	Colorectal cancer
NCR	National Cancer Registry
ASR	Age-standardised incidence rate
CT	Computed tomography
FOBT	Faecal occult blood test
IFOBT	Immunochemical faecal occult blood test
gFOBT	Guaiac faecal occult blood test
FIT	Faecal immunochemical test
WCE	Wireless capsule endoscopy
CCE-1	First Generation Colon Capsule Endoscopy
CCE-2	Second Generation Colon Capsule Endoscopy
GI	Gastrointestinal
USPSTF	United States Preventive Services Task Force
ACS	American Cancer Society
MSTF	Multi-Society Task Force on Colorectal Cancer
ACR	American College of Radiology
DCBE	Double-contrast barium enema
FS	Flexible sigmoidoscopy
CTC	Computed tomographic colonography
US FDA	United States Food & Drug Administration
AFR	Adaptive frame rate
mm	millimetre
DR3	Data Recorder 3
MRI	Magnetic resonance imaging
PEG	polyethylene glycol
NaP	sodium phosphate
RCT	Randomised controlled trial
CASP	Critical Appraisal Skills Programme
WHO	World Health Organization
PPV	Positive predictive value
NPV	Negative predictive value
ROC	Receiver operating characteristics
OR	Odd ratio
ICER	Incremental cost-effectiveness ratio
RCT	Randomised controlled trial
SR	Systematic review
RR	Relative risk
CI	Confidence interval
SD	Standard deviation
ICER	Incremental cost-effectiveness ratio
QALY	Quality adjusted life years

HEALTH TECHNOLOGY ASSESSMENT (HTA)
CAPSULE ENDOSCOPY FOR COLORECTAL CANCER SCREENING

1 BACKGROUND

Colorectal cancer (CRC) is a term used for cancer that starts in the large intestine; in the colon or in the rectum. Alternatively, these cancers can also be referred separately as colon cancer or rectal cancer. The colon has four sections; ascending colon, transverse colon, descending colon and sigmoid colon while the rectum is the final 6 inches of the digestive system (Figure 1). More than 95% of colorectal cancers are a type of cancer known as adenocarcinomas which develop slowly from a growth of tissue or polyp on the inner lining of the colon or rectum over a period of 10 to 20 years (Figure 2).[1] These polyps can be non-pre-cancerous such as hyperplastic polyps and inflammatory polyps, or pre-cancerous polyps such as adenomatous polyps (adenomas) are that can undergo malignant transformation into cancer. Epidemiologic evidence suggests that dietary and lifestyle factors including high intake of red and processed meat, low level of physical activity, obesity and smoking increase risk of CRC, but the impact of modifying these risk factors is not established.[2-4]

Figure 1: Anatomy of large intestine

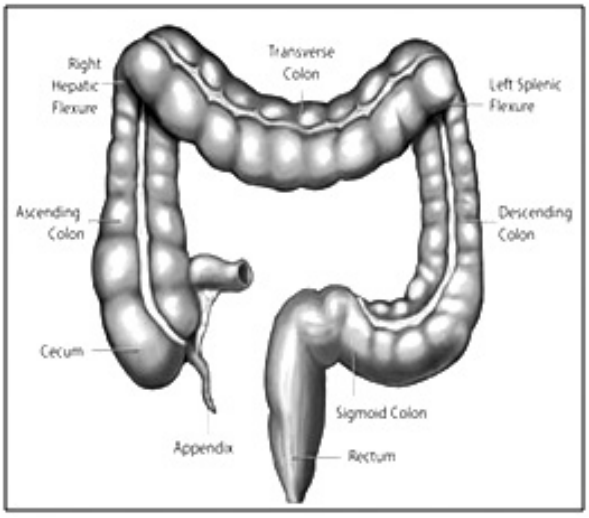
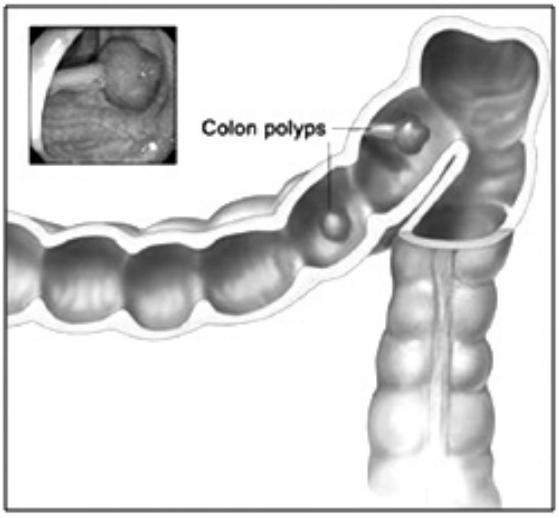


Figure 2: Colonic polyps



Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008.[5] In a systematic review and meta-analysis of 8 studies, Spada et al. reported that the overall prevalence of polyps of any size and significant findings at colonoscopy (the reference standard) was 57% (399 cases) and 27.4% (221 cases).[6] In Malaysia, colorectal cancer (CRC) is the commonest cancer among men and the second most common cancer among women.[7] A total of 2,246 cases were diagnosed in 2007 and reported to NCR, represent 12.3 % of all cases reported. The incidence of colorectal cancer in 2007 was slightly higher among males with age-standardised rate (ASR) of 13.4 per 100,000 population compared to females (ASR 10.2 per 100,000 population).[7] The incidence was highest among Chinese where the ASR for males and females were 19.4 and 14.6 per 100,000 populations respectively.[7] It is the third commonest cause of cancer-related mortality that one out of three patients suffering from CRC will not survive.[6] One of the main reasons for the high mortality is the high proportion of advanced stage at presentation.[6]

CRC is a largely preventable disease which requires community participation in the prevention process, such as life style modification and proper screening, early detection and removal of adenomatous polyps (precancerous polyps).[8] In 2008, the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology jointly issued guidelines for the detection of adenomatous polyps and CRC in asymptomatic, average-risk adults.[9] While these guidelines recommend screening to start at 50 years old, the age to stop screening is unclear.

The latest, updated Asia Pacific Consensus Recommendations for Colorectal Cancer Screening specifies the age range for CRC screening as 50 to 75 years.[4] Low risk individuals are those below the age of 50 years while average risk individuals are those who aged 50 years and above. Individuals at increased risk of CRC include: individuals with 1) history of adenomatous polyps; 2) personal history of curative-intent resection of CRC; 3) family history of either CRC or colorectal adenomas diagnosed in a first degree relative 4) history of inflammatory bowel disease of significant duration; or 5) known or suspected presence of one of 2 hereditary syndromes, specifically hereditary non-polyposis colon cancer (Lynch syndrome) or familial adenomatous polyposis.[4]

Screening tests are grouped into those that primarily detect cancer and those that can detect cancer and adenomatous polyps, thereby increasing the potential for CRC prevention through polypectomy (Table 1).[3] Cancer prevention tests have the potential to image both cancer and polyps, whereas cancer detection tests have low sensitivity for polyps and typically lower sensitivity for cancer compared with that in cancer prevention tests.

Table 1: Testing Options for the Early Detection of CRC and Adenomatous Polyps[3]

Tests That Detect Adenomatous Polyps and Cancer

- flexible sigmoidoscopy (FS)
- colonoscopy
- double contrast barium enema (DCBE)
- CT colonography (CTC)

Tests That Primarily Detect Cancer

- annual gFOBT (Guaiac faecal occult blood test)
- annual IFOBT (Immunochemical faecal occult blood test) or FIT (Faecal immunochemical test)
- stool DNA

Alternatively, these tests can be categorised into stool-based and structural exams of the colon (Table 2).[10] Colonoscopy is considered the gold standard of colorectal cancer screening methods for its ability to view the entire colon and both detect and remove polyps during the same procedure.

Table 2: Screening guidelines in the USA for average-risk individuals10

	USPSTF	ACS/MSTF/ACR
Stool-based tests		
Standard gFOBT	sensitive FOBT preferred	not recommended
Sensitive gFOBT	annual	annual
FIT	annual	annual
Stool DNA	not recommended	recommended; interval uncertain
Structural exams of colon		
CT colonography	not recommended	every 5 years
Double-contrast barium enema	not recommended	recommended only if other tests not available; every 5 years
Flexible sigmoidoscopy	every 5 years	every 5 years
Flexible sigmoidoscopy + high-sensitivity FOBT	FS every 5 years FOBT every 3 years	FS every 5 years FOBT annually
Colonoscopy	every 10 years	every 10 years
Overall recommendations		
Type of test	any test	structural exam of colon preferred
Age to start screening	50 years	50 years
Age to stop screening	age 75–84: individualize age >85: not recommended	no age specified

USPSTF = US Preventive Services Task Force
ACS = American Cancer Society
MSTF = Multi-Society Task Force on Colorectal Cancer
ACR = American College of Radiology

In Malaysian setting, mass population screening is not yet available that most of the patients presented late and many cancer cases are diagnosed from symptomatic patients.[11] Currently, opportunistic screening program using various methods including faecal occult blood test (FOBT), flexible sigmoidoscopy and colonoscopy are in place.[12] Studies done locally have shown that CRC awareness and preventive activities are still poor among Malaysian.[13] Study conducted by Harmy et al. (2013) which examined colorectal cancer screening participation and its barriers among average risk individuals in Malaysia showed that only 0.7% of patients had undergone any of the CRC screening methods in the past five years.[14] The main patient and test factors for not participating were embarrassment (35.2%) and feeling uncomfortable (30.0%), respectively. There were 11.2% of respondents who never received any advice for screening. In those who had screening, being advised by health care providers (84.6%) was the main factor. The same authors also found extremely low knowledge and attitude towards colorectal cancer screening among moderate risk patients.[15] Norwati et al. (2014) found low level of CRC preventive activities among Malaysian primary health care provider.[16] It may be related to the low availability of the test in health centres, providers not using more updated recommendation and poor awareness and understanding about the importance of colorectal cancer screening among patients. FOBT is in fact easily available and free in Malaysian health care facilities but only few health clinics have this test. In most of the primary care health clinics, the test needs to be sent to nearest hospital laboratory and because of that it become tedious and not commonly ordered. This indicates that many of the primary care providers are not aware that the availability of FOBT in their setting.[16]

Colonoscopy is considered the gold standard of colorectal cancer screening methods for its ability to view the entire colon and both detect and remove polyps during the same procedure.[4, 9, 17] Most guidelines recommend colonoscopy to be done 10 yearly as the preferred cancer prevention test and annual faecal immunochemical test (FIT) as the preferred cancer detection test.[4, 9, 17] However, no more than 25% compliance has been achieved in the screening programs.[15] This low compliance can be explained by the drawbacks of conventional colonoscopy, such as being painful, patient's embarrassment or the need for sedation.[4]

There is therefore a need for an additional safe, minimally invasive method for visualizing the colon that might serve as an additional screening method for the early detection of colorectal cancer and adenomatous polyps.[18] Capsule endoscopy is a new technology with evolving indication for CRC screening. On the basis of the technological development and the previous clinical experiences with the small bowel capsule endoscope, the colon capsule endoscope (CCE) offers an alternative non-invasive technique that allows exploration of the colon without requiring sedation and air insufflations.[17]Therefore, a Health Technology Assessment (HTA) is required to assess the diagnostic accuracy, safety, effectiveness and cost-effectiveness of capsule endoscopy for CRC screening in adult population.

This HTA was requested by the Head of Clinical Research Centre, Sultanah Bahiyah Hospital, Alor Setar, Kedah who is also the National Advisor of the Gastroenterology Services of Malaysia.

2 TECHNICAL FEATURES

2.1 THE WIRELESS CAPSULE ENDOSCOPY (WCE) SYSTEM

Wireless capsule endoscopy (WCE) provides visualization of the gastrointestinal tract via single-use ingestible capsule designed to acquire video images during natural propulsion through the digestive system. The vast majority of WCE systems in the market are for visualization of the small bowel. The first capsule model for the small intestine was approved by the Food and Drug Administration (FDA) in 2001. Over subsequent years, this technology has been refined to provide superior resolution, increased battery life, and capabilities to view different parts of the GI tract including oesophagus and colon. In 2006, Given Imaging Ltd, Yoqnaem, Israel launched their first generation of CCE, PillCam COLON Capsule Endoscopy System (CCE-1) and the much improved second generation of PillCam COLON 2 Capsule Endoscopy System (CCE-2) in 2010. To date, PillCam COLON is commercially available in more than 80 markets including Japan, Europe, Latin America, Canada, Australia, Asia and Africa with its data validated in more than 34 publications.[20]

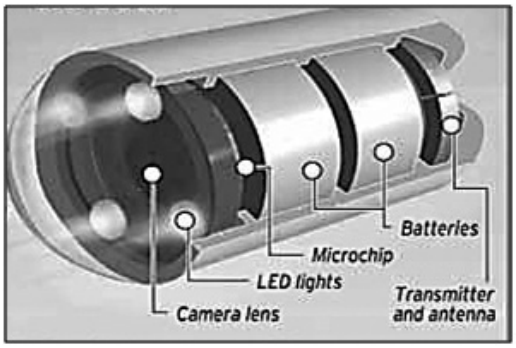
To date, there are various brands of capsule endoscopy being marketed worldwide but thus far Given Imaging's PillCam COLON is the only one received FDA approval for imaging the large intestine in any application (Table 3).[19]

Table 3: A survey of pill endoscopy providers[19]

Institute	Model	Target	Size(mm^2)	Duration	Rate	Sensor	Etc.
Given Imaging (Israel)	PillCam ESO2	esophagus	11 x 26	20 min.	18 fps	2 CMOS	
	PillCam SB2	small intestine	11 x 26	8 hrs.	2 fps	CMOS	256x256 pixel
	COLON	large intestine	11 x 31	10 hrs.	4 fps	2 CMOS	
Olympus (Japan)	Endo Capsule	small intestine	11 x 26	8 hrs.	2 fps	CCD	Real-Time Video Stream
RF System Lab. (Japan)	NORIKA 3	small intestine	9 x 23	WPT	30 fps	CCD	rotation
	Sayaka	small intestine	9 x 23	WPT	30 fps	CCD	2MB/mm^2
Jinshan S&T (China)	OMOM	small intestine	11 x 25.4	7 hrs.	30 fps	CMOS	
KIST (Korea)	MIRO	small/large intestine	11 x 24	11 hrs.	3 fps	Micro optic.	320x320 pixel, RTVS

The WCE system consists of 3 components: (1) a capsule endoscope; (2) a sensing system with sensing pads or a sensing belt to attach to the patient, a data recorder, and a battery pack; and (3) a personal computer workstation with proprietary software for image review and interpretation. The capsule endoscope consists of an optical dome, a lens, several light emitting diodes (LED), a semiconductor, transmitter, and an antenna (Figure 3).

Figure 3: A capsule endoscope



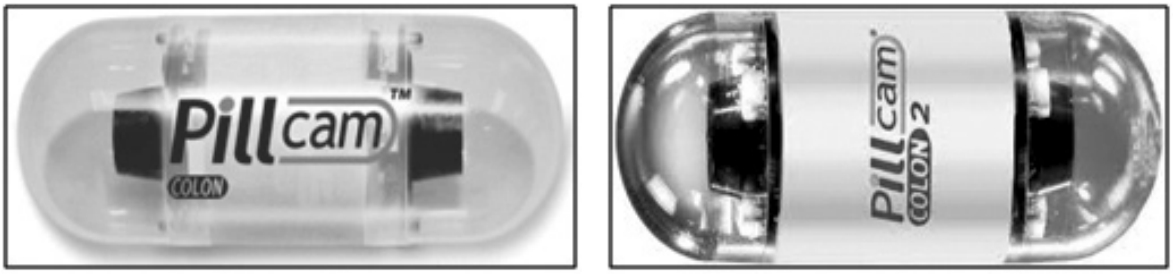
2.1.1 First Generation Pillcam® Colon Capsule Endoscopy System (CCE-1)

PillCam® COLON (Given Imaging Ltd, Yoqneam, Israel) first generation capsule endoscopy (CCE-1) uses a small, wireless camera contained in an easy-to-swallow and disposable capsule the size of a large vitamin, specifically designed to visualize the colon for the detection of polyps (Figure 4). The envelope of the capsule is made of biocompatible materials, sealed with biocompatible adhesives.[20] The capsule measures 31 by 11 mm and has two imagers that enable it to acquire video images from both ends. The angle of view from each imager is 156 degrees. It has a total operating time of 10 hours and acquires images at a rate of 4 frames per second (2 for each imager) when virtually stationary and 35 images per second when in motion.[20, 21] At the beginning of the examination, CCE turns on and transmits images for 3 min before it enters a “sleep” mode for 1 h and 45 min to save battery energy. After this time, it automatically switches on and reactivates in the terminal ileum, allowing a complete colonic exploration.

2.1.2 Second Generation PillCam® COLON 2 Capsule Endoscopy System (CCE-2)

The second generation of colon capsule endoscopy is similar to the first generation CCE and consists of a slightly bigger, ingestible video capsule (Figure 4). The CCE-2 has 2 imagers with a much wider angle of view that has been increased to 172 degrees per imager, allowing nearly 360 degrees coverage of the colon by two. The most unique feature of the CCE-2 is its adaptive frame rate (AFR). This new technology allows the CCE-2 to capture 35 images per second when in motion and 4 images per second when virtually stationary.[20] CCE-2 has been provided with a new portable wireless data recorder able to automatically identify when the CCE enters into the small bowel. It also has a user-friendly interface, sending active, customised reminders to the patient, mainly in relation to the different laxative booster intakes after capsule ingestion and when the procedure ended.[20]

Figure 4: PillCam® Colon Capsule 1 and PillCam® Colon Capsule 2



2.2 THE HARDWARE[20]

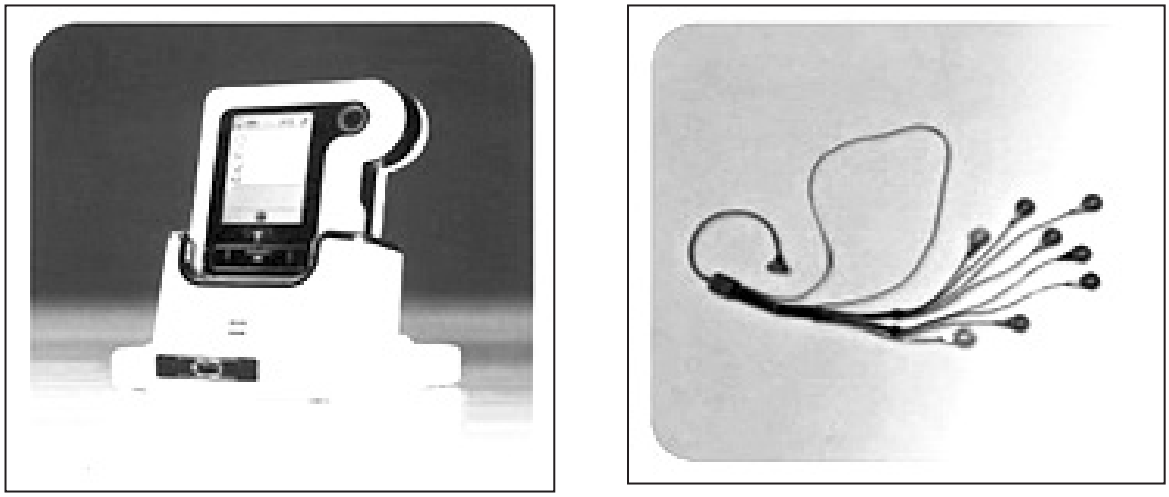
2.2.1 PillCam® Recorder[20]

The PillCam recorder is a small portable recording device that communicates with the PillCam capsules as the capsule passes through the GI tract (Figure 5). The recorder is placed in the recorder pouch which is attached to the sensor belt and worn around the patient's waist. After the procedure the data is downloaded from the PillCam recorder for physician review. The new revolutionary Data Recorder 3 (DR3) used with CCE-2, has smart features that allows bidirectional communication between DR3 and the capsule. The former receives optical information from the capsule, performs online analysis and send out corresponding instructions to the capsule such as to raise the transmission rate to 35 images per second when the capsule is in motion. DR3 also communicates with the patient if and when to take a prokinetic agent, to shorten gastric transit time and moves the capsule into small bowel. It also notifies the patient on when to ingest the first and or second booster laxative or when to insert a Bisacodyl suppository and finally notifies when the patient may eat and that the procedure is over.

2.2.2 PillCam® Sensor Belt[20]

The sensor belt is a comfortable belt worn around the patient's waist over clothing (Figure 5). It employs easy-fasten straps for quick adjustment and removal. The sensors incorporated within the belt eliminate the need for inconvenient adhesive sensor sleeves and reduce patient prep time and equipment maintenance.

Figure 5: PillCam recorder DR3 and Pillcam sensor array



2.2.3 RAPID® Real-time Viewer[20]

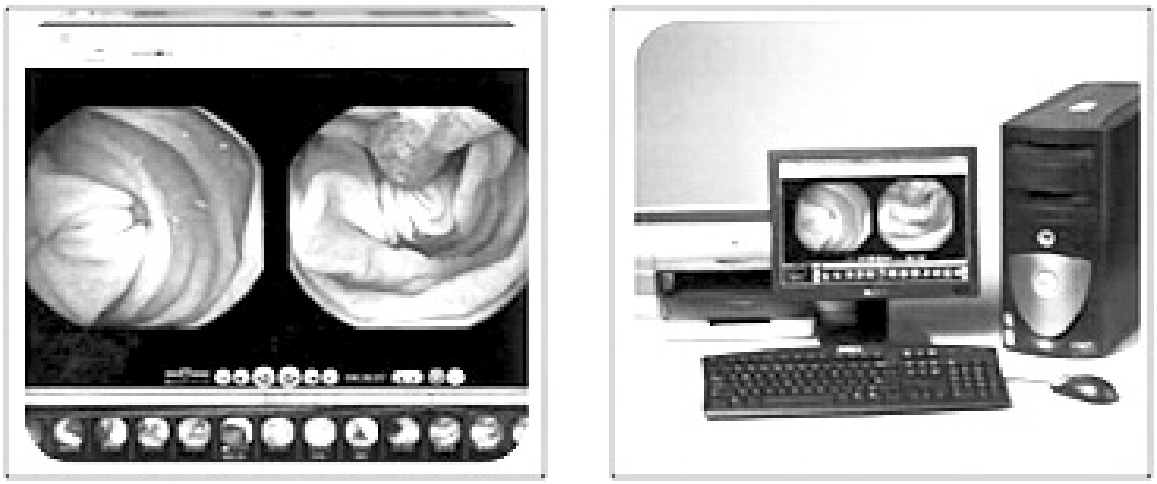
RAPID Real-time viewer is a handheld device that enables real-time viewing during a PillCam procedure. The handheld device also contains the complete RAPID Reader software.

2.3 THE SOFTWARE[20]

RAPID for PillCam Software v8

The latest CCE-2 uses RAPID software v8 which has a new user-friendly interface and software features to review and interpret RAPID videos on the main RAPID workstation as well as on another computer system (Figure 6).

Figure 6: RAPID for PillCam software and RAPID workstation



2.4 INDICATIONS[20]

PillCam® COLON capsule endoscopy is indicated for direct visualization of the colon, including identifying the occurrence of polyps. It is complementary to colonoscopy and may be used as an alternative for those who refuse other invasive colon exams or in some patients who have higher risk for complications from colonoscopy including patients with bleeding, or sedation risks, previous incomplete colonoscopy or for patients with inflammatory bowel disease.

2.5 PROCEDURE RISKS AND CONTRAINDICATIONS[20]

Procedure Risks

Risk associated with CCE procedures include capsule retention, capsule aspiration, skin irritation and risk being near any source of powerful electromagnetic fields. Capsule retention is defined as having a capsule that remains in the digestive tract for more than two weeks. If the patient fails to see passage of the capsule or the study does not show a clear exit of the capsule to the caecum, an X-ray may verify if the capsule is retained. Capsule aspiration while patients are attempting to swallow a capsule is rare. There is also a low risk of skin irritation from the PillCam® sensor array's sleeve adhesive or silicone exposure. After ingesting a PillCam® capsule and until the capsule is excreted, patients should not be near any powerful electromagnetic fields, such as one created by an MRI device.

The risks associated with colon preparation are potential allergies or other known contraindication to any preparation agents or medications used for the CCE regimen.

Contraindications

- Patients with known or suspected GI obstruction, strictures, or fistulas based on the clinical picture or pre-procedure testing and profile
- Patients with cardiac pacemakers or other implanted electro-medical devices
- Patients with swallowing disorders

2.6 THE PROCEDURE

A day prior to the exam, the patient is advised to maintain a liquid diet and to adhere to a bowel preparation regimen specifically designed for the CCE procedure. In general, both CCE-1 and CCE-2 utilise similar bowel preparation procedures. Similar to colonoscopy, a clean colon is achieved by the consumption of a clear liquid diet and 4 litre of polyethylene glycol (PEG) in a split-dose fashion prior to colon capsule ingestion. In CCE, however, the bowel preparation is also required to help promote capsule propulsion distally through the bowel. For this reason, adding 1 or 2 doses of sodium phosphate boosters (NaP) followed by another litre of water helps to accelerate colon capsule transit through both the small and large bowel within the operating time of the capsule battery.[21] The following morning, the patient arrives at the physician's office, where they are prepared for the exam. This includes attaching the sensor array or sensor belt to the patient's abdomen and the data recorder to a belt around the patient's waist. After this, the patient is given a glass of water to help swallow the pill and up to an additional three cups of cleansing agents during the procedure. As the sedation is not required, patients can leave the clinic or office after ingestion and continue normal daily activities. Visual and auditory alerts are provided to ensure patient compliance with physician instructions and enables patients to complete the procedure outside of the clinic. After six to twelve hours the procedure is completed. At that time, the data recorder and sensors are returned. The pill passes naturally with a bowel movement usually within 24 hours. Oral intake can occur within hours of swallowing the pill. Images are downloaded from the data recorder by the physician to a computer with proprietary RAPID software for review.

According to European Society of Gastrointestinal Endoscopy (ESGE) Guideline (ESGE, 2012), the CCE reporting should indicate the quality of preparation, technical details of the examination, completeness of the procedure, and on the significant findings (polyps/masses measuring 6mm or more, 3 or more polyps, irrespective of size).[17] Extracolonic findings should also be reported when clinically meaningful. Patients found to have a polyp measuring 6mm or more at CCE, as well as those with three or more polyps irrespective of size, should be sent for colonoscopy for polypectomy. Patients without significant findings at CCE should repeat CCE or a different screening test after five years, unless bowel preparation at CCE was inadequate.[17]

2.7 COMPETING TECHNOLOGIES

Virtual endoscopy such as Computed Tomographic Colonography (CTC) is a new method of diagnosis using a radiological imaging to produce two- and three-dimensional images of the entire colon and rectum. The procedure allows visualization of areas distal to an obstructed or twisted bowel, providing information on occlusive carcinomas. In addition, CTC is able to define the exact anatomic location of abnormalities and the proximity of adjacent structures, whereas conventional colonoscopy only estimates the location of lesions.[22] CTC requires full bowel preparation and expensive equipment for the test. 'Faecal tagging' may be used, which requires the patient to ingest an iodinated contrast agent with meals approximately 48 hours before the scan. Sedation is not usually required for CTC. The colon is distended by insufflation with air or carbon dioxide via a small rectal tube. In a meta-analysis study which include 49 studies assessing the sensitivity of both CTC and colonoscopy for colorectal cancer detection, CTC was found to be highly sensitive, especially when both cathartic and tagging agents are combined in the bowel preparation.[22] Data on 11,151 patients with a cumulative colorectal cancer prevalence of 3.6% (414 cancers) showed sensitivity of CTC for colorectal cancer to be 96.1% (398 of 414; 95% CI; 93.8 - 97.7).

The sensitivity of colonoscopy for colorectal cancer, derived from a subset of 25 studies including 9223 patients, was 94.7% (95% CI; 90.4 - 97.2%).[22] CTC is currently recommended by the several guidelines as the imaging modality of choice in cases of incomplete colonoscopy.[17, 23]

2.8 REFERENCE OR 'GOLD STANDARD

Colonoscopy is currently considered the gold standard for detection of colorectal neoplasia, allowing for a high rate of detection of potentially curable CRCs and precancerous adenomatous polyps.[9] The advantage of colonoscopy is that it enables detection, biopsy, and removal of identified lesions in a single, convenient session. The efficacy of colonoscopy has been demonstrated by many studies, with more recent studies found the long term benefits of colonoscopic polypectomy in reducing CRC mortality by 53% to 68%.[24] The drawback of the technique is that it is invasive and is associated with clinically important complications such as bleeding and/or perforation, but the likelihood of these risks are small and they are more commonly associated with polypectomy and/or biopsy. It is also associated with discomfort/pain and embarrassment.[25]

3 POLICY QUESTION

Should capsule endoscopy be used to screen adult population for colorectal cancer?

4 OBJECTIVES

4.1 To determine the diagnostic accuracy of capsule endoscopy for CRC screening in adult population compared with conventional colonoscopy.
4.2 To assess the safety of capsule endoscopy compared with conventional colonoscopy in CRC screening.
4.3 To determine the effectiveness of CRC screening using capsule endoscopy compared with conventional colonoscopy, with regards to patient outcomes such as detection rate, cancer mortality rate, quality of life and quality adjusted life years (QALY) gained.
4.4 To determine the economic implication of using capsule endoscopy compared with conventional colonoscopy for CRC screening.
4.5 To assess the ethical, legal, and organizational aspects related to CRC screening using capsule endoscopy.

Research Questions

i. How accurate is capsule endoscopy compared to conventional colonoscopy in CRC screening?
ii. How safe is capsule endoscopy compared with conventional colonoscopy in CRC screening?
iii. How effective is capsule endoscopy compared with conventional colonoscopy in CRC screening?
iv. What are the economic implications of using capsule endoscopy compared with conventional colonoscopy for CRC screening?
v. What are the ethical, legal, and organizational issues related to CRC screening using capsule endoscopy?

5 METHODS

5.1 LITERATURE SEARCH STRATEGY

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2014,EBM Reviews - Health Technology Assessment 4th Quarter 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 2014, EBM Reviews - Cochrane Central Register of Controlled Trials November 2014, EBM Reviews - ACP Journal Club 1991 to November 2014, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2014. Parallel searches were run in PubMed and Embase. Search was also conducted through some official websites such as World Health Organisation (WHO), US FDA, INAHTA, CADTH and MHRA. General database such as Google was used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. Appendix 3 showed the detailed search strategies. Limit on adult population was applied to the search. The last search was run on 30 November 2014.

5.2 STUDY SELECTION

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1 Inclusion criteria

a. Population : Adults, aged more than 18 years old

b. Intervention : Capsule endoscopy

c. Comparators : Conventional colonoscopy

d. Outcome :
i. Polyp detection rate, adenoma detection rate, cancer detection rate, any pathology (e.g. diverticula) detected, mortality rate, survival rate, quality of life, and quality adjusted life years (QALY) gained.
ii. Diagnostic accuracy: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of capsule endoscopy.
iii. Adverse events related to the use capsule endoscopy as a CRC screening test.
iv. Cost, cost-benefit, cost-effectiveness, and cost utility of using capsule endoscopy for CRC screening.

e. Study design : HTA reports, systematic review, randomised controlled trial (RCT), diagnostic accuracy studies, cross-sectional, cohort, case-control, and economic evaluation studies

f. Publication : Full text articles

5.2.2 Exclusion criteria

a. Hereditary colorectal cancer
b. Animal study
c. Narrative review
d. Laboratory study

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. If it was unclear from the title and / or the abstract, the full text article was retrieved. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3 QUALITY ASSESSMENT STRATEGY

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool by two reviewers.[26] For meta-analysis or systematic review, the criteria assessed include selection of studies, assessment of quality of included studies, heterogeneity of included studies. For diagnostic accuracy, criteria being assessed include the measured diagnostic performance / accuracy in comparison with the standard reference. For economic evaluation, the criteria assessed include comprehensive description of competing alternatives, effectiveness established, effects of intervention identified, measured and valued appropriately, relevant resources and health outcome costs identified, measured in appropriate units and valued credibly, discounting, incremental analysis of the consequences and costs of alternative performed and sensitivity analysis performed. The CASP checklist is as in Appendix 5. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).[27]

5.4 DATA EXTRACTION STRATEGY

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by another reviewer. Disagreements were resolved by discussion. Details on:(1) methods including study design, (2) study population characteristics including gender, age, (3) type of intervention, (4) comparators, (5) type of outcome measures were extracted. The extracted data were presented and discussed with the expert committee.

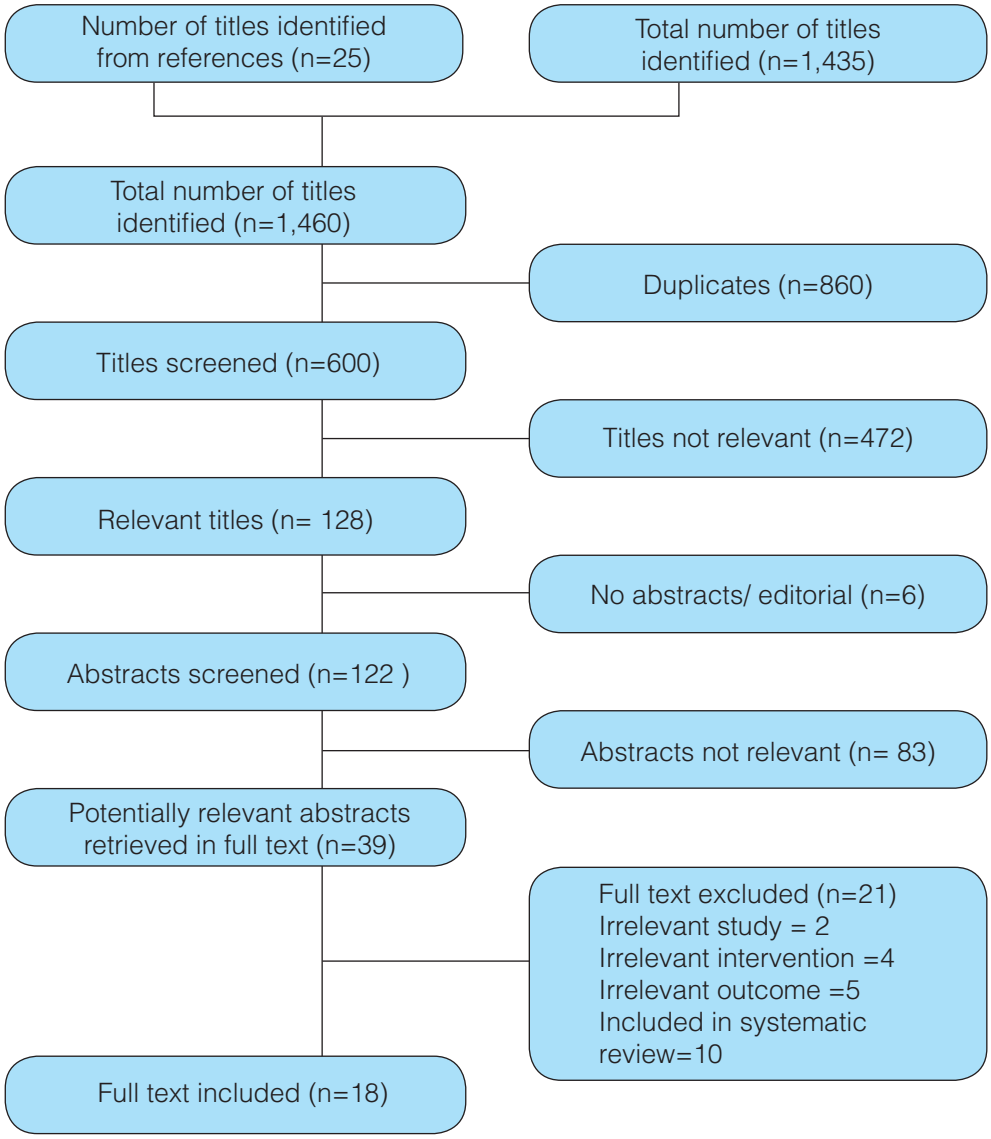
5.5 METHODS OF DATA SYNTHESIS

Data on the safety, efficacy and cost implication of using capsule endoscopy for colorectal cancer screening were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6 RESULTS

A total of 1435 titles were identified through the Ovid interface: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Database of Abstracts of Reviews of Effects 4th Quarter 2014,EBM Reviews - Health Technology Assessment 4th Quarter 2014, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 2014, EBM Reviews - Cochrane Central Register of Controlled Trials November 2014, EBM Reviews - ACP Journal Club 1991 to November 2014, EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2014, EMBASE 1988 to 2014 and PubMed. Twenty five titles were retrieved from the references. After removal of 860 duplicates, 600 titles were screened. A total of 128 titles were found to be potentially relevant and 122 abstracts were screened using the inclusion and exclusion criteria. Thirty nine potentially relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the full text articles, 18 full text articles were included and 21 full text articles were excluded. The articles were excluded due to irrelevant study, irrelevant intervention, irrelevant outcome and already included in a systematic review report. The 18 full text articles finally selected for this review comprised of three meta-analyses which include one HTA report on capsule endoscopy for colorectal cancer screening, one cost-effectiveness analysis and 14 observational studies. The articles were published between 2008 and 2014. The studies were mostly conducted in the European countries including Israel, Belgium, Spain, Germany, Italy, France, United Kingdom and Switzerland as well as in the USA.

Flow Chart of Study Selection



Risk Of Bias

In the meta-analyses studies, Quality Assessment of Diagnostic Accuracy in Systematic Reviews (QUADAS) was used by the authors to assess the risk of bias within the included studies and funnel plot was used to assess the risk of bias across the studies. The funnel plot did not show a meaningful symmetry and the Egger test was not significant. Observational studies however, have potentially higher risk of bias.

6.1. DIAGNOSTIC ACCURACY AND EFFECTIVENESS

Nine articles (studies) related to the diagnostic accuracy and effectiveness of capsule endoscopy for screening for colorectal cancers were included in the review. There were three meta-analyses which include one Health Technology Assessment (HTA) report and six observational studies. Six articles were related to the first generation capsule endoscopy (CCE-1) while three articles were related to the second generation capsule endoscopy (CCE-2). The outcome measures included accuracy of the instrument as well as the detection rate of colorectal polyp and or cancers.

6.1.1a Diagnostic Accuracy Of First Generation Capsule Endoscopy (Cce-1)

A meta-analysis was conducted by Spada et al. (2010) to assess the accuracy of CCE-1 in detecting colorectal polyps.[6, Level I] The eight studies that were included in the meta-analysis are shown in Table 4. The meta-analysis provided data on 837 patients with average or increased risk of CRC with only two studies enrolled solely asymptomatic subjects. The median age of 57.5 years, ranged between 54–60 years with slightly more than half (57%) of the participants were males. Study design was similar in all of the included studies, in which CCE-1 performance was compared against post-CCE colonoscopy, with the endoscopists blinded to CCE results. The study defined clinically significant findings as polyps 6 mm or larger and/or when more than 3 polyps were present, irrespective of polyp size. Prevalence of polyps and significant findings were 57% and 27.4%, respectively. CCE sensitivity and specificity for polyps of any size were 71% (95% CI, 66%–76%) and 75% (95% CI, 66%–83%), respectively. CCE sensitivity and specificity for significant findings were 68% (95% CI, 56%–79%) and 82% (95% CI, 77%–85%), respectively. CCE identified 16 of the 21 cancerous lesions detected by colonoscopy (pooled sensitivity 76%).

Rokkas et al. (2010) performed a meta-analysis to examine the data of existing CCE trials to determine the yield and miss rate of CCE.[28, Level I] A total of 7 studies were included with a total of 626 asymptomatic, average and increased risk of CRC individuals (Table 4). For any polyp found, per-patient CCE sensitivity of 73% (95% CI, 68%-77%) and specificity of 89% (95% CI, 81%-94%). The area under the curve (AUC) under the sROC (weighted symmetric summary receiver operating curve) was 0.7965. For significant polyps, per-patient CCE sensitivity and specificity were 69% (95% CI, 62%-75%) and 86% (95% CI, 82%-90%). Heterogeneity in sensitivities was not observed among the studies (Cochran *Q* test = 2.76, df = 5, *P* =0.74,I^2= 0%). Specificities were heterogeneous (*Q* test =0. 32, df = 5, *P* =0 .000, I^2 = 84.4%). The AUC for the sROC was 0.7886.

Another meta-analysis was conducted by the Ontario Ministry of Health and Long Term Care and published in their Health Technology Assessment (HTA) Report.[29, Level I] Two studies were included in this meta-analysis (Table 4) which enrolled individuals 50 years and older who were asymptomatic, as well as having increased risk of CRC. No study heterogeneity was identified across the two studies. For the detection of significant polyps (defined as >6 mm or ≥3 polyps), the pooled sensitivity was 73% (95% CI; 54%–87%) and pooled specificity was 92% (95% CI; 84%–97%). Incremental yield (IY) is calculated by substracting the yield of colonoscopy from yield of CCE. For the detection of 'any polyp', CCE had a 57% yield compared with 61% yield for colonoscopy [IY, –0.05 (95% CI; –0.18 to 0.07), *p* = 0.4, Heterogeneity: Chi^2 = 0.03, df = 1 (p = 0.85), I^2 = 0%. For detection of significant polyps, CCE had a 31% yield compared with a 29% yield for colonoscopy with a IY of 0.05 (95% CI; –0.14 to 0.24, p = 0.6 Heterogeneity: Chi^2 = 2.48, df = 1 (p = 0.12), I^2 = 59.7%.

Table 4: Main characteristics of included studies in 3 Meta-analyses[6, 28, 29]

Study	Country	Patients n	Mean age	Patients included		Asymptomatic patients n (%)
				n (%)	Inclusion criteria	
Eliakim et al. 2006[a,b,c]	Israel	91	57	84(92)	Average and increased risk	58(69)
Schoofs et al. 2006[a,b,c]	Belgium	41	56	36(88)	Average and increased risk	17(41)
Van Gossum et al 2009[a,b]	Europe	332	58	320(96)	Increased risk	0(0)
Sieg et al. 2009[a,b]	Germany	38	56	36(95)	Asymptomatic	36(100)
Spada et al.2008 [a]	Italy	40	58	40(100)	Average and increased risk	18(45)
Gay et al. [a]	France	128	55	126(98)	Average and increased risk	74(58)
Sacher-Huvelin et al. [a,b]	France	105	60	105(100)	Asymptomatic	105(100)
Pilz et al.[a]	Switzerland	62	59	59(95)	Average and increased risk	30(54)
Lewis et al. [b]	USA	25	NR	25	NR	NR
Costamagna et al. [b]	Italy	20	NR	20	NR	NR

All studies used PillCam® Colon 1 (Given Imaging Ltd.Yognaem, Israel), NR = not reported
[a] included in Spada et al.[6]
[b] included in Rokkas et al.[28]
[c] included in Ontario HTA Report[29]

In a prospective, multicentre trial, Sacher-Huvelin et al. (2010) compared CCE-1 and colonoscopy among 545 subjects with average (asymptomatic individuals aged 50–74 years) and increased risk (asymptomatic patients with a personal or family history of CRC or polyps, without colonoscopy during the preceding three years) (Table 5). [30, Level 1] This study was conducted prospectively in 16 French academic centres. Overall, colonoscopy detected more patients with polyps than did CCE. For polyp any size, 311 (57%) patients were detected by colonoscopy compared with 249 seen at CCE (46%; $p < 0.0001$) while for polyps ≥6 mm and ≥10 mm, the corresponding figures were 112 (21%) vs. 94 (17%) ($p = 0.097$) and 43 (8%) vs. 29 (5%) ($p = 0.03$) respectively. Five patients with CRC were detected by colonoscopy compared with only three detected by CCE. The two missed cancers were located in the sigmoid colon and rectum, and both were relatively large tumours (35 mm and 15 mm respectively). The CCE accuracy of detection of polyps ≥6 mm or CRC was 39% (95% CI 30–48) for sensitivity, 88% (95% CI; 85–91) for specificity, 47% (95% CI; 37–57) for the positive predictive value (PPV) and 85% (95% CI; 82–88) for the negative predictive value (NPV). The authors did not establish non-inferiority of CCE as compared with colonoscopy for the detection of polyps ≥6 mm either for sensitivity [absolute difference 51% (95% CI; −58 to −43)] or for NPV [absolute difference −13% (95% CI; −16 to −10)]. For 118 patients, the results of CCE and colonoscopy were discordant concerning the primary criterion of judgment. All of the CCE videos of these discordant cases were reviewed by the expert panel. The reinterpretation of the capsule videos improved the diagnostic yield of CCE, with sensitivity increasing to 57% (95% CI; 48–66), specificity to 95% (95% CI; 93–97), PPV to 73% (95% CI; 63–82) and NPV to 90% (95% CI; 87–92). For advanced adenomas, the sensitivity of CCE was better, at 72%, and an NPV of 94%.

Herrerias-Gutierrez et al. (2011) conducted a prospective study in Spain which enrolled a total of 144 subjects between 18 and 80 years of age who had been referred for colorectal cancer screening, control after polipectomy or suffered digestive symptoms (rectal bleeding, anaemia or diarrhoea) (Table 5).[31, Level 2] The mean age (± SD) of the subjects was 52.17 (±16.71) years with 67 women and 77 men. The physician performing the capsule procedure and reading the capsule and the physician performing the conventional colonoscopy study were blinded to the other technique. Compared to colonoscopy, the rate of agreement was 75,6%, the sensitivity was 84% and the specificity 62.5%, PPV was 77.7% and NPV was 71.4 %. The exploration with CCE was completed in 134/144 cases (93%), without any case of retention. Concerning the detection of polyps, CCE detected 19 polyps (two of them not detected by colonoscopy) and colonoscopy detected 19 polyps (two of them not detected by CCE). In four cases CCE was positive with negative colonoscopy. Two cases were diverticulosis and two had angiodysplasia that was not seen by colonoscopy.

Pilz et al. (2010) conducted a prospective, single-centre pilot study in Switzerland to evaluate CCE method for performance as a screening tool compared to colonoscopy in asymptomatic patients under routine screening conditions (Table 5).[32, Level 3] A total of 56 patients (34 male, 22 female) participate in this study with mean age of 60 years, median 59 years, range 38-84 years, with 86% were of age 50 years or older. Inclusion criteria included age of 50 years without symptoms or with lower gastrointestinal signs and symptoms, individuals younger than 50 years with positive family history for CRC. Significant polyp was defined as polyp size >5 mm. Polyp detection rate (per-patient) was 50% (n = 28) for colonoscopy and 62% (n = 35) for CCE. Significant size polyps were diagnosed in six patients (11%) on colonoscopy, 15 patients (27%) on CCE. Eleven percent (n = 6) of patients had polyps of any size on colonoscopy that were not detected on CCE. 13/56 (23%) patients had findings of any size on CCE that were not verified on colonoscopy, two (4%) were of significant size. For polyps of any size, CCE showed a sensitivity of 79% (95% CI; 61 to 90), specificity 54% (95% CI; 35 to 70), PPV of 63% and NPV of 71% for polyps of any size. For overall polyp size, detection of polyps on CCE and on colonoscopy was independent with statistical significance (p = 0.013), indicating differences in the detection rate for polyps on both examinations. For significant polyps (>5 mm) there was a correspondence in the detection rates of both methods (p > 0.05). The sensitivity was 50% (95% CI; 19 to 81), the specificity was 76% (95% CI; 63 to 86), the PPV was 20% and the NPV was 93%. Per-patient-prevalence of adenoma was 27% (n = 15) on colonoscopy. Numbers are too small to calculate for sensitivity and specificity, but all (n = 3) of the detected tubulo-villous adenoma were detected by CCE. Tubular adenoma were detected in 18% (a total of 10 patients on colonoscopy, all size), one the two detected tubular adenoma of significant size on colonoscopy was classified as ≤5 mm on CCE. One of the two detected serrated adenoma was not seen on CCE. No high-grade dysplasia or cancerous lesion was found on either type of examination.

Table 5: Studies reporting performance measures for first generation colon capsule endoscopy in colorectal cancer screening

Study	Centre	Patients • Total included • Mean age • Inclusion criteria	Accuracy % (95% CI) Polyp ≥6mm				Polyp/ Cancer Detection % (95% CI)
			Sensitivity	Specificity	PPV	NPV	
Spada et al. (2010)[6]	Multicentre and Single centre studies	• N=837 • Mean age: 57.5 years • average and increased risk	Pooled 68 (56–79)	Pooled 82 (77–85)	NR	NR	Cancer detection (Pooled) 76 (58-94)
Rokkas et al.. (2010)[28]	Multicentre and Single centre studies	• N = 626 • Mean age ± SD: 50 ± 8.9 years • Asymptomatic, increased risk	Pooled 69 (62-75)	Pooled 86 (82-90)	NR	NR	NR
Medical Advisory Secretariat (2009)[29]	Multicentre and Single centre studies	• N=132 • Age range : 26-75 • Asymptomatic, increased risk	Pooled 73 (54-87)	Pooled 92 (84-97)	Individual studies 40-46	Individual studies 83-88	Incremental yield **Any polyp= -0.05(-0.18-0.07) Significant polyp= 0.05(-0.14 -0.24)
Sacher-Huvelin et al. (2010)[30]	Multicentre	• N= 545 • Mean age: 60 (25-86) • Average and increased risk	39 (30–48)	88 (85–91)	47(37-57)	85(82-88)	Polyp detection: 46%
Herrer as Gutiérrez et. al. (2011)[31]	Single centre	• N=144 • Mean age: 52.2±16.7 years • Screening for CRC,post polypectomy, symptomatic	84	62.5	77.7	71.4	
Pilz et al. (2010)[32]	Single centre	• N=56 • Median age: 59 • Average and increased risk	50 (19-81)*	76(63-86)*	20*	93*	Polyp detection: 27%

All studies used PillCam® Colon 1 (Given Imaging Ltd.Yognaem, Israel)
*polyp > 5mm
**Incremental yield (IY)= yield of CCE minus yield of colonoscopy

6.1.1b Diagnostic accuracy of second generation capsule endoscopy (CCE-2)

Eliakim et al. (2009) conducted a feasibility study involving 5 centres in Israel (Table 6).[33, Level 1] A total of 104 patients scheduled for colonoscopy and having known or suspected colonic disease were enrolled with their mean age 49.8 years. Second-generation capsule endoscopy was prospectively compared with conventional colonoscopy as gold standard for the detection of colorectal polyps and other colonic disease. CCE-2 detected polyps of any size in 45 patients (46% of patients); of these,35 (36% of patients) had polyps ≥ 6mm including 17 patients(17% of patients) with polyps ≥ 10 mm. In addition to polyps, CCE-2 detected diverticulosis in 9 patients and erythema/inflammation in 7 (78 %) and 3 (75 %) of these patients respectively. The capsule sensitivity for the detection of patients with polyps ≥ 6mm was 89% (95% CI; 70–97) and for those with polyps ≥ 10mm it was 88% (95 %CI 56–98). Its specificities for the detection of patients with polyps ≥ 6mm and with polyps ≥ 10mm were 76% (95 %CI; 72–78) and 89% (95 %CI; 86–90), respectively.

Spada et al.(2011) in a prospective multicentre trial involving eight European sites compared the feasibility, accuracy, and safety of CCE-2 with colonoscopy (Table 6).[34, Level 1] A total of 117 patients were recruited with their mean age ± SD = 60 ± 9 years. Patients were of average or increased risk of colorectal neoplasia. Data from 109 patients were analyzed. Colonoscopy was independently performed (blinded to the results of CCE-2) within 10 hours after capsule ingestion or on the next day. No unblinding of colon capsule endoscopy results at colonoscopy was carried out. Overall polyp detection rate (regardless of size) at colonoscopy and CCE-2 was 84% and 81%, respectively. CCE-2 correctly classified 35 and 28 of these patients, corresponding to a detection rate for ≥6 mm and ≥10 mm neoplasia of 90% (95% CI; 80%-99%) and 93% (95% CI; 84%-100%), respectively. Per-patient CCE-2 sensitivity of CCE-2 for polyps ≥6 mm and ≥10 mm was 84% and 88%, with specificities of 64% and 95%, respectively. At colonoscopy, a total of 45 patients (41.3%) had at least one polyp measuring ≥6 mm. Thirty-two patients (29.3%) had at least one polyp that was ≥10 mm.

Hagel et al. (2014) conducted a prospective trial which enrolled in total, 24 patients (14 male, 10 female) with an average age of 51 years (range 24 to 75 years) (Table 6).[35, Level 3] Indications for CRC screening include personal or family history of CRC or adenomatous polyps, with no previous colonoscopy within three years and those who were scheduled to undergo colonoscopy for known or suspected colonic diseases. CCE-2 was performed first, followed by colonoscopy the day after. The recorded CCE videos were interpreted by two investigators who are highly experienced with small bowel capsule endoscopy and specifically trained for CCE. Colonoscopy was performed by experienced endoscopists in all cases. They were blinded to the capsule reader's results. CCE accuracy for detecting polyps (per-finding analysis) revealed in 6 of 23 cases, both colonoscopy and CCE did not detect polyps (true negative). In the other 17 cases, 47 polyps were detected. Forty of 47 (85.1%) polyps were apparent in both examinations (true positive). Four (8.5%) polyps were detected by colonoscopy but missed at CCE (false negative). Three (6.4%) polyps were detected by CCE: size 3 mm and 7 mm, and 11 mm in the cecum or the ascending colon but not reconfirmed at colonoscopy (false positive). One of these three polyps (3 mm) was located in the cecum and could not be identified by colonoscopy even after unblinding of the endoscopist for this finding. However, three of the latter seven polyps were recorded in patients who had more than one polyp, which were all detected by both methods. According to this per-finding analysis, CCE achieved an overall sensitivity of 90.9% (95% CI; 85% to 100%) and a specificity of 67.6% (95% CI; 36% to 98%) in the detection of any size polyp. Compared with colonoscopy, polyps were found by CCE with a PPV and NPV of 93.0% and 71.4%, respectively. In the per-patient analysis, CCE could identify patients with polyps regardless of the number or size with a sensitivity of 81.5% (95% CI; 62% to 100%) and a specificity of 85.7% (95% CI; 60% to 100%). The PPV of CCE with respect to identifying patients with colorectal polyps was 92.9% while the NPV was 67%.

Table 6. Studies reporting diagnostic accuracy for second generation colon capsule endoscopy (CCE-2) in colorectal cancer screening

Study	Centre	Patients	Accuracy % (95% CI) Polyp ≥6mm				Polyp/ Cancer Detection % (95% CI)
			Sensitivity	Specificity	PPV	NPV	
Eliakim et al. (2009)[33]	Multicentre	• N = 104 (98 analysed) • Mean age=49 (range 18-57) • Increased risk	89 (70-97)	76 (72-78)	NR	NR	Polyp 46%
Spada et al. (2011)[34]	Multicentre	• N = 117 (109 analysed) • Mean age= 60 ± 9 years • Average and increased risk	84 (74-95)	64 (52-76)	NR	NR	Polyp 81% Cancer ≥6mm 90% (80%-99%) ≥ 10mm 93% (84%-100%)
Hagel et al. (2014)[35]	Single centre	• N = 24 • Mean age= 51yrs (range 24-75) • Average and increased risk	90.9 (85-100)	67.6 (36-98)	93	71.4	Polyp 87.1%

All studies used PillCam® Colon 2 (Given Imaging Ltd.Yognaem, Israel)

6.1.2 CRC Mortality

There was no retrievable evidence on reduction in mortality rate, quality of life and quality adjusted life-years gained related to screening of CRC using capsule endoscopy.

6.2 SAFETY

Seven articles (studies) reported complications or adverse events related to the use of capsule endoscopy for colorectal cancer screening.[6,30,32-36] Complications were either procedure-related or bowel-preparation related complications. The former included complications related to the capsule endoscopy procedure or to the system (data recorder or belt) while the latter included bowel preparation and medications. These complications were all mild in nature. There was no reported tracheal aspiration or death related to capsule endoscopy reported in any of the studies.

6.2.1 Safety of CCE-1

Four articles reported complications or adverse events related to CCE-1 for colorectal cancer screening. Spada et al. (2010) reported CCE failure in reaching the colon within the limited operating time in 2.3% patients (95% CI; 1.2%–3.4%).[6, Level I] Incomplete CCE colonoscopy was reported in 13% of cases. Twenty nine cases of mild/moderate side effects (ie, nausea, abdominal pain) corresponding to a rate of 4.1% (95% CI; 2.6%–5.6%) were reported.

Sacher-Huvelin et al. (2010) reported 19 mild adverse events. No severe adverse event was related to the capsule itself. Comparison of VAS scores showed a slight (probably not clinically relevant) statistical difference in favour of CCE compared with colonoscopy (8.74 ± 1.56 vs. 8.25 ± 2.00; $p < 0.0001$).[30, Level 1]

Pilz et al. reported one patient who had an allergic skin reaction to the adhesive tape of the electrodes during CCE. One patient presented with abdominal pain after polypectomy (during colonoscopy).[32, Level 3]

Triantafyllou et al. (2014) reported 10% of patients reported mild adverse events (AE) which include nausea, vomiting and mild abdominal discomfort.[36, Level II-3]

PillCam® COLON 1 has received a CE Mark in 2006, but was not cleared for marketing or available for commercial distribution in the U.S.A., Japan, and certain other countries.[20]

6.2.2 Safety of CCE-2

Three articles (studies) reported complications or adverse events related to CCE-2 used for colorectal cancer screening. Spada et al. (2011) reported 8 out of 117(6.8%) mild to moderate adverse events were reported which resolved spontaneously within 24 to 48 hours. [34, Level 1] Five were related to bowel preparation and included vomiting, nausea, and abdominal pain while two experienced fatigue because of the long capsule procedure. One patient experienced severe adverse event (colon perforation after polypectomy) not related to colon capsule endoscopy.

Eliakim et. al. (2009) reported no adverse events that directly related to capsule or colonoscopy procedures.[33, Level 1] The capsule excretion rate in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). There were overall eight adverse events (8 %) in seven patients. Seven were related to the preparation: five were mild-moderate headaches/nausea which resolved within 24 hours and two were mild vomiting which resolved within 48 hours. One patient had urinary retention, rated as a severe adverse event unrelated to the study.

Hagel et al. (2014) reported one patient reported headache during preparation for the CCE procedure.[35, Level 3] Otherwise no other adverse events were recorded during the CCE and the colonoscopy.

CCE-2 claimed to have received clearance from US FDA under the direct de novo classification for devices with low to moderate risk.[20]

6.3 ECONOMIC EVALUATION

6.3.1a Economic evaluation of CCE-1

Cost effectiveness analysis

There was one retrievable cost-effectiveness analysis (CEA) study of capsule endoscopy in colorectal cancer screening conducted by Hassan et al. (Table 7).[37, Level I] The cost–effectiveness of two screening strategies using colonoscopy or capsule endoscopy were compared based on a Markov process. In the model, a hypothetical population of 100,000 individuals aged 50 years and over, undergoes a 10 yearly screening procedure. Different thresholds for postcapsule polypectomy referral were simulated. The number of life–years saved by screening corresponds to the difference in life–years lost from CRC between a Markov model and one without screening, or between two different screening strategies. The incremental cost–effectiveness ratio (ICER) between two strategies, including the possibility of no screening, was defined as the difference in cost divided by the difference in life–expectancy, which represents the cost per life–year gained. Both future costs and future life–years saved were discounted using an annual rate of 3%. An incremental cost–effectiveness ratio of $ 100,000 per life–year gained was used as the threshold to differentiate an efficient procedure from an inefficient procedure. One– and two–way sensitivity analyses were performed for all the variables of the model.

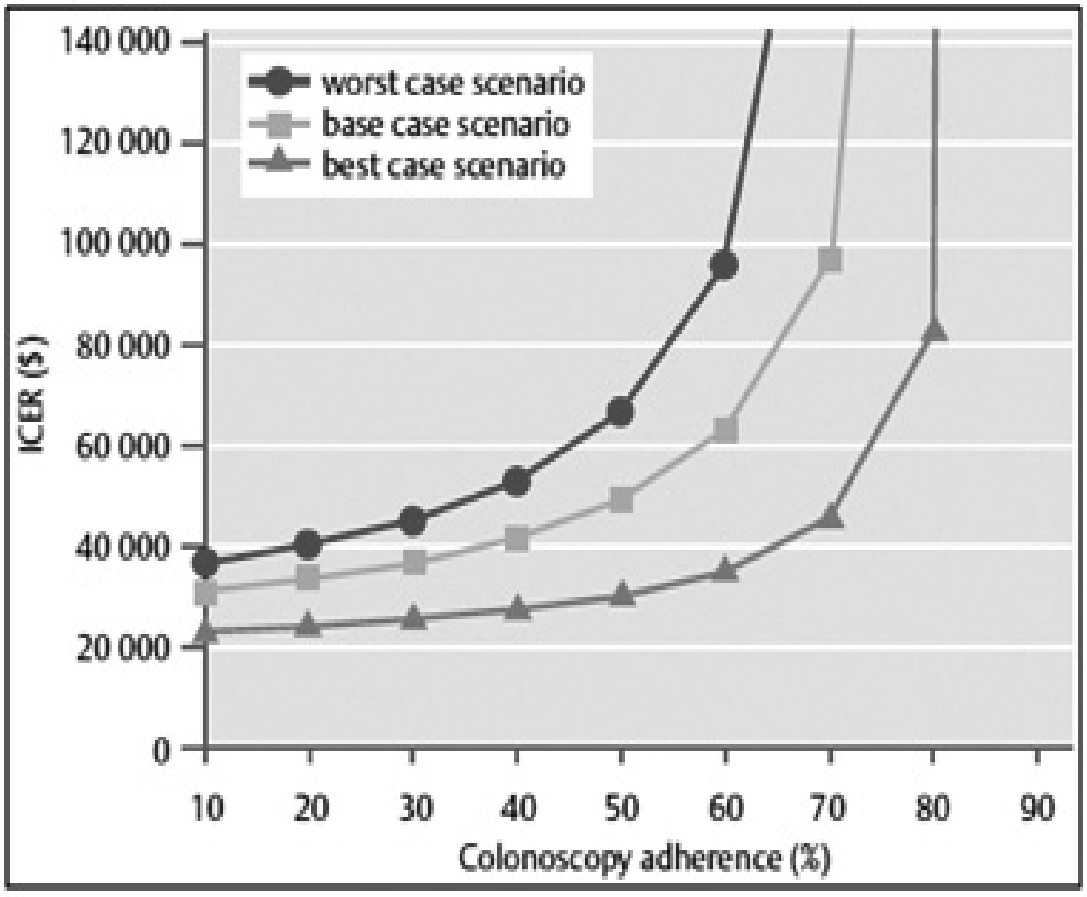
When compared with no screening, each strategy resulted in a decrease of CRC–related costs, averting substantial economic resources that would have been spent for the surgical and oncological treatment of the unprevented CRC (Table 7).[37] At baseline, the incremental cost–effectiveness (compared with no screening) of colonoscopy and capsule endoscopy was $ 16,165 and $ 29,244 per life–year saved, respectively. A 6mm threshold for polypectomy referral was associated with a substantial cost reduction in the capsule endoscopy program.

Table 7: Main outcomes of model[37]

Variable	None	Capsule endoscopy	Capsule endoscopy (6 mm threshold)	Colonoscopy
CRC prevented, n	-	3713	3244	4312
CRC prevention rate, %	-	63	55	72.6
Life-years saved, n	-	8927	8255	10669
Procedures, n				
Capsule endoscopies	-	299955	304426	-
Colonoscopies	-	186117	98084	395252
Diagnostic (without polypectomy)	-	128717	78822	326176
Therapeutic (with polypectomy)	-	57400	19262	69076
Complications, n				
Bleeding events	-	276	92	317
Perforations	-	140	68	232
Costs, US$				
Capsule endoscopy	-	243374623	246141525	-
Colonoscopy	-	139435425	69606876	316554877
Care for CRC	204319642	82560910	96154795	60241370
Total	204319642	465370958	411903196	376796247
ICER vs. no screening	-	29244	25147	16165

When equal compliance was simulated, the colonoscopy program was more effective and less costly than a strategy based on capsule endoscopy. When simulating an initial compliance to capsule endoscopy 30% better than colonoscopy, capsule endoscopy became the more effective and more cost–effective option. A 20% better compliance was sufficient when a higher accuracy of capsule endoscopy for polyps was assumed (Figure 7).

Figure 7: Incremental cost-effectiveness of CCE compared with colonoscopy according to different compliance curves[37]



The cost of a capsule was reported to be around RM 1,688.25[38] (USD 500; 1 USD = RM 3.37).[39]

6.3.1b.Economic evaluation of CCE-2

There was no retrievable article that evaluates cost-effectiveness of CCE-2 in CRC screening.

6.4 ORGANIZATIONAL ISSUES

6.4.1 Patient acceptance and uptake of capsule endoscopy

In a prospective study performed in Germany to examine whether colon capsule endoscopy could increase adherence to screening colonoscopy in a healthy population, Groth et al. (2012) simulated the uptake of any endoscopic screening test (capsule or conventional colonoscopy) by the project invitation letters to be 5.8% (124/2150), with 34 (1.6%) opting for primary colonoscopy and 90 (4.2%) choosing primary capsule endoscopy.[40, Level 3]Comparing these rates to the spontaneous rate set at 1%, the increase was 60% for colonoscopy (1.6% versus 1%, $p = 0.075$; two sided comparison) and more than 4 fold (4.2% versus 1%; $p < 0.001$) for capsule colonoscopy. In other words, offering capsule endoscopy led to a fourfold increase of screening uptake compared to standard colonoscopy. Regarding sex distribution, uptake was 5.6% in men and 2.8% in women ($p = 0.002$). Amongst those persons who eventually underwent one of the two tests, the main reason for a final choice of capsule was the fear of colonoscopy-related discomfort and complications, while the main reason for choosing colonoscopy was the possibility for taking tissue samples and carrying out polypectomy. Among participants in the capsule group who were asked whether capsule colonoscopy would be again the method of choice for repeated colonic examination, 65% answered “yes” and 22% “probably yes”, after capsule colonoscopy. The corresponding values for colonoscopy were 94% and 0%. Twenty two persons who underwent colonoscopy after capsule, 16 answered the questionnaire and 11 stated they would choose conventional colonoscopy for a repeat examination, mainly because everything could be done in one procedure and colonoscopy was felt to be more accurate. Two further persons said that they would probably choose capsule rather than conventional colonoscopy.

Pilz et al. (2012) reported that 21 (40%) patients preferred CCE to colonoscopy, while 20 (38%) preferred colonoscopy and 12 (23%) had no preference.[32, Level 3] Fifty (94%) patients would recommend CCE. Fourty four (83%) subjects would prefer to undergo a capsule colonoscopy again in ten years’ time for screening purposes compared to eight patients (15%) who declined and one patient (2%) who was indecisive. Sixteen patients (30%) felt restricted during daily-life activities by carrying the electrodes and the recorder.

In terms of acceptability of CCE-2, Negreanu et.al. (2013) in a prospective, single center study assessed the feasibility, accuracy and acceptability of CCE-2 in detection of significant lesions in at risk CRC patients, unable or unwilling to perform colonoscopy because of the anaesthetic risk and co-morbidities.[41, Level 3] A total of 70 patients at risk of colorectal cancer were enrolled in the study with mean age 58.3 years (range 29 to 87). CCE-2 showed positive findings in 23 patients (34%, 95% CI; 21.6%-44.1%). Every patient accepted CCE-2 as an alternative exploration tool and 65 out of 70 (93%) agreed to have CCE-2 in future.

6.4.2 Training

Identification of landmarks, interpretation of pathology, and formulation of appropriate management advice are essential information in reporting a CCE video.[42] It requires much longer reading times than colonoscopy, usually ranges between 30 and 60 min.[43] Its interpretation is largely dependent on the expertise and experience of the gastroenterologist reviewing the images.[42] Familiarity with the capsule hardware and software is also necessary.

Inter-rater agreement

Jang et al. (2010) in a systematic review evaluated inter-observer variation associated with capsule endoscopy interpretation by experts compared to trainees.[44, Level I] The findings showed that the inter-observer differences were greatest for subtle lesions which were often missed by trainees and that experience with conventional endoscopy is important in reviewing CCE findings.

Pezzoli et al. (2011) evaluated inter-observer agreement in the description of capsule endoscopy findings.[45, Level II-3]In this study, consecutive short segments of capsule endoscopy were prospectively observed by eight investigators. Seventy five videos were prepared by an external investigator (gold standard). The description of the findings was reported by the investigators using the same validated and standardized capsule endoscopy structured terminology. The agreement was assessed using Cohen's kappa statistic. The agreement with the gold standard was moderate (kappa 0.48), as well as the agreement relating to the final diagnosis (kappa 0.45). The best agreement was observed in identifying the presence of active bleeding (kappa 0.72), whereas the poorest agreement concerned the lesion size (kappa 0.32). The agreement with the gold standard was significantly better in endoscopists with higher case or volume of capsule endoscopy per year. Correct lesion identification and diagnosis seem more likely to occur in presence of angiectasia, and for readers with more experience in capsule endoscopy reading.

6.4.3 Bowel preparation and cleanliness

The main issue regarding CCE acceptability in a screening setting is represented by the tolerability and safety of the preparation. A CCE procedure requires more extensive bowel preparation than colonoscopy. Unlike colonoscopy, CCE is not equipped with rinse and suction techniques that can be used to remove turbid fluids. The rigorous bowel cleansing required for CCE with 4 litre PEG and laxatives may prevent it from being used in healthy people. In patients with impairment of renal function, the use of sodium phosphate (NaP) booster might be associated with electrolyte abnormalities due to the absorption of phosphate.[46]

According to European Society Gastrointestinal Endoscopy (ESGE) guideline, colon cleanliness can be graded by using a 4-point scale (excellent or good [adequate], fair or poor [inadequate]) for each of the following colonic segments: cecum, right colon, transverse colon, left colon, rectosigmoid colon (Table 9).[17]

Table 9 : Cleansing level scale[17]

Rating	Description
Poor	Inadequate Large amount of faecal residue precludes a complete examination
Fair	Inadequate but examination completed Enough faeces or turbid fluid to prevent a reliable examination
Good	Adequate Small amount of faeces or turbid fluid not interfering with examination
Excellent	Adequate No more than small bits of adherent faeces

Van Gossum et al. examined the effect of the level of cleanliness on the accuracy of lesion detection during capsule endoscopy.[18, Level 2] They found that sensitivity was significantly higher in the patients with good or excellent cleanliness as compared with the patients with poor or fair cleanliness, with a limited effect on specificity. The sensitivity and specificity for the detection of polyps (≥6 mm) in the 59 patients with good or excellent cleanliness were 75% (95% CI; 65 to 83) and 84% (95% CI; 80 to 87), respectively, and for the detection of such polyps in the 26 patients with poor or fair cleanliness,

the sensitivity and specificity were 42% (95% CI; 28 to 56) and 84% (95% CI; 78 to 90), respectively. For patients with advanced adenoma, the sensitivity and specificity in the 33 patients with good or excellent cleanliness were 88% (95% CI; 74 to 95) and 78% (95% CI; 76 to 79), respectively, and in the 16 patients with poor or fair cleanliness, the sensitivity and specificity were 44% (95% CI; 25 to 64) and 81% (95% CI; 77 to 85), respectively.

Sacher-Huvelin et al. (2010) also found that CCE accuracy was better in the group of patients with good or excellent cleanliness compared with those with poor or fair preparation.[30, Level 2]In the well-prepared patients, the NPV increased to 88% (95% CI; 83–92) for polyps ≥6 mm and 98% (95% CI; 96–99) for polyps ≥10 mm, but sensitivity remained low [53% (95% CI; 39–67) for polyps ≥6 mm].

6.4.4 Out of clinic setting

Adler et. al. (2014) conducted a cohort study of 41 patients who underwent CCE-2 as an out of clinic study.[47, Level II-3] Forty one patients (29 men) with a mean age of 57 years, with known or suspected colonic diseases who had up to 40 min of travel time from clinic to home were offered CCE-2 as an out-of-clinic procedure. Lesions size 6 mm or larger were detected in 10 (24 %) of the 41 patients. Nine of these patients (90 %) underwent a workup colonoscopy within a few months after the colon capsule procedure. The findings of CCE-2 were confirmed in all cases. One patient with a lesion larger than 18 mm reported by CCE-2 eventually had a 25-mm sigmoid adenocarcinoma diagnosed. As an out-of-clinic procedure, CCE2 is feasible and easily performed. A home-based procedure may be associated with better acceptability and potentially with increased adherence to colorectal cancer screening.

6.4.5 Colonoscopy failure/ incomplete colonoscopy

Triantafyllou et. al. (2014) conducted a prospective, follow-up study in three tertiary-care centres to investigate the extent that CCE complements incomplete colonoscopy and guides further workup 75 outpatients.[36, Level II-3] A total of 75 patients were recruited consecutively as outpatients after colonoscopy failure. They were follow-up for two years. One third of the patients underwent CCE immediately after colonoscopy. Overall, in 68 patients (91%), CCE reached or went beyond the colon segment at which colonoscopy stopped. CCE technically complemented difficult colonoscopy of whether same-day CCE was performed (24 [96%]) or was not performed (44 [88%]). CCE detected additional significant findings in 36% of the same-day CCE cases and in 48% of the rescheduled ones. Two patients in the same-day group and 13 in the rescheduled CCE group underwent further colon examination that revealed additional significant findings in 3 of them. 63 participants (84%) were willing to repeat CCE, if needed. Follow-up has not identified symptomatic missed colon cancers. The authors concluded that CCE performed immediately or at a scheduled date after colonoscopy failure was feasible and safe.

In a prospective study conducted in 17 French centers**,** Pioche et al. (2012) tested the diagnostic yield of CCE-1 in incomplete or temporarily contraindicated cases.[48, Level 2] Inclusion criteria were colonoscopy failure or general disease that is contraindicated for anaesthesia. The main end point was CCE diagnostic yield, defined as identification of a colorectal lesion that directly explained symptoms or necessitated a diagnostic or therapeutic examination. CCE showed positive findings in 36 patients (diagnostic yield 33.6 %), among whom 23 subsequently underwent therapeutic intervention. Among 64 patients with negative capsule findings, nine had a complementary procedure showing adenomas in only one case. CCE was incomplete in 7 out of 107 patients. Colonoscopy was done in one patient to retrieve a capsule retained in the left colon, and sigmoidoscopy in 11 because the rectum was not reached. No colorectal cancer was diagnosed during the follow-up period.

6.5 COMPETING TECHNOLOGIES

A prospective, single-blinded study was conducted by Spada et al. (2014) to evaluate the role of capsule endoscopy (CCE-2) and CT Colonography in patients with a previous incomplete colonoscopy.[49, Level 2]A total of 100 patients (66 female, median age 59 years, range 33–75 years) were prospectively enrolled. CTC was performed after colon capsule excretion or 10–12 hours post-ingestion. In cases where positive findings (polyps/mass lesions ≥6 mm) were found on either test, colonoscopy was then performed. Since colonoscopy was performed only in positive cases, diagnostic yield and positive predictive values of CCE and CTC were used as study end-points. In a per-patient analysis for polyps ≥6 mm, CCE-2 detected 24 patients (24.5%) and CTC detected 12 patients (12.2%). The relative sensitivity of CCE compared to CTC was 2.0 (95% CI; 1.34 - 2.98), indicating a significant increase in sensitivity for lesions ≥6 mm. in terms of larger polyps (≥10 mm), these values were 5.1% for CCE and 3.1% for CTC (relative sensitivity: 1.67 (95% CI; 0.69 to 4.00)). Positive predictive values for polyps ≥6 mm and ≥10 mm were 96% and 85.7%, and 83.3% and 100% for CCE and CTC, respectively. No missed cancer occurred at clinical follow-up of a mean of 20 months. Both CCE-2 and CTC were found to have comparable efficacy in completing colon evaluation after incomplete colonoscopy with the overall diagnostic yield of colon capsule was superior to CTC.[49]

6.6 ETHICAL IMPLICATION

In this review, false positive rates for capsule endoscopy ranged from 12% to 33% for CRC, respectively.[6, 28, 30, 34] False positive results expose healthy people to unnecessary intervention and alarm, as well as generating considerable additional costs.

7 DISCUSSION

The purpose of this HTA is to evaluate whether, and under what conditions, capsule endoscopy would be effective, safe, and cost-effective for CRC screening to be used among the general population in Malaysia.

Overall, the studies that assessed diagnostic accuracy or performance of capsule endoscopy showed that it was effective in the detection of polyps or CRC among patients in the average and increased risk of CRC. For first generation CCE (CCE-1), PPV ranged from 20 – 77%, NPV ranged from 71 - 93% while sensitivity and specificity ranged from 68 - 84% and 62 - 92%, respectively.[6, 28-32] The diagnostic yield of the first generation CCE ranged from 27 – 76%. These rates substantially improved with the second generation CCE (CCE-2), with sensitivity and specificity, 84 – 90% and 64 – 76%, respectively.[33-35] For adults with known or suspected colonic diseases, there was evidence of low to fair quality indicating that CCE-2 achieved relatively high accuracy for detection of colorectal polyps. These rates were higher than the 50 % cut-off for sensitivity that has been adopted by the American Cancer Society to define a test acceptable for screening purposes.[50] The effectiveness of CCE on mortality rate, survival rate or quality of life however, was not known due to the paucity of evidence.

CCE-1 sensitivity was suboptimal when compared with colonoscopy. However, in a screening setting, population adherence to colonoscopy was disappointingly low, ranging from 10% to 26%, that the apparently higher accuracy of colonoscopy is reduced by such a low compliance. On the other hand, CCE is potentially more attractive than colonoscopy because it is non-invasive, sedation-free, painless and safe. Studies found good acceptability towards CCE compared to colonoscopy where offering capsule endoscopy led to a fourfold increase of screening uptake compared to standard colonoscopy.[40]Therefore, CCE could compensate its lower accuracy with a higher attendance rate in a screening setting, as shown in a model simulation study.[37] So it is concluded that the cost-effectiveness of capsule endoscopy depends mainly on its ability to improve compliance to CRC screening.

Diagnostic accuracy of CCE was influenced by level of bowel cleanliness, as well as readers' experience.[17, 18, 30, 43]A CCE procedure requires more extensive bowel preparation than colonoscopy. The challenge is to determine an effective bowel preparation regime without causing nephrotoxicity. This procedure also requires much longer reading times than colonoscopy.[43] CCE reading time and interpretation were found to be largely dependent on the expertise and experience of the gastroenterologist reviewing the images.[33] This could make a mass CCE screening less feasible and applicable.

In terms of cost-effectiveness of CCE in screening for CRC, CCE was found to be cost-effective when compared to no screening. It became a non-cost-effective alternative when its uptake is assumed equal to that of colonoscopy. However, CE became an efficient option when it was assumed that uptake of CCE would be higher than that of colonoscopy for CRC screening. In other words, cost-effectiveness of CRC screening using CCE will mainly depend on its ability to improve compliance. When compliance to capsule is 30% better than colonoscopy, capsule is more effective and most effective option. 20% better compliance was enough if detection accuracy was better.

Colonoscopy is the most comprehensive option, but in some individuals, achieving a complete colonoscopy may not be possible. Patients with incomplete colonoscopy incur additional costs along with the inconvenience and risk of other procedures to complete colorectal examination. For this reason, non-invasive tests may be proposed in this setting as an alternative to colonoscopy. Among non-invasive imaging tests, CCE may be applicable in the context of screening because of the abovementioned considerations of feasibility, safety and accuracy. For those individuals, CCE could be an effective option to allow their gastroenterologist to complete a colon examination.[47]

The use of CCE could be highly desirable in a national population based screening programme such in Malaysian setting where the uptake and compliance to current screening method is low[14, 51] CCE has consistently shown to be a very safe procedure: no major complication has been reported in several studies with no radiation-related risk.[6, 18, 28, 32, 35] On the other hand, no data was available on the possible uptake of CCE in the context of a general population screening. All these studies were based on disease-enriched populations, mainly consisting of symptomatic patients. CCE sensitivity compares favourably with the other non-invasive or less-invasive options for CRC screening. Compared to CTC, CCE showed a higher diagnostic yield for significant polyps (*i.e.,* polyps ≥ 6 mm).[49] Differently from CT, however, CCE is not associated with the risk of radiation-induced cancer, and this may represent an undeniable advantage in a screening setting. Randomized studies comparing CCE with radiological imaging or conventional endoscopic modalities are needed to confirm the efficacy of CCE in this setting. CCE also appears to be a feasible procedure, which can be done as an out-of-clinic (home-based) procedure,[47] with a very low rate of technical failures and a high capsule excretion rate up to 90%.[6, 18, 28-30] However, the sensitivity and specificity of capsule endoscopy were highly variable that its usage as a home-based procedure could not be recommended.

Limitations

This systematic review of literature has several limitations. There was no RCT conducted to assess the performance related to capsule endoscopy. The observational studies mostly have unclear risk of biases. Generalizability and international comparisons of an economic evaluation are very limited. There was no retrievable study done among Malaysian population. Although there was no restriction in language during the search but only English full text articles were included in the report.

8 CONCLUSION

8.1 DIAGNOSTIC ACCURACY AND EFFECTIVENESS

In first generation capsule endoscopy (CCE-1), there was fair to good level of evidence on the diagnostic accuracy or performance of capsule endoscopy which showed that it was effective in the detection of polyps in patients with average risk (asymptomatic patients aged 50 years and above) and increased risk of CRC (individuals with personal and family history of adenomatous polyps or CRC, history of inflammatory bowel disease or those diagnosed with hereditary non-polyposis colon cancer or familial adenomatous polyposis). [6, 28-32]

a. Sensitivity and specificity ranged from 68 - 84% and 62 - 92% respectively
b. PPV ranged from 20 – 77% and NPV ranged from 71 - 93%.
c. The diagnostic yield of the first generation CCE ranged from 27 – 76%.

In second generation capsule endoscopy (CCE-2), there was also fair to good level of evidence that suggested its accuracy in detecting polyps and CRC among the average and increased risk patients. For the detection of polyps, CCE-2 showed sensitivity and specificity of 84 – 90% and 64 – 76%, respectively while its detection rate for CRC ranged from 90% to 93%.[33-35]

The accuracy of CCE-1 was found to be suboptimal as compared to colonoscopy. There was wide variations in the sensitivity, specificity, positive predictive value and negative predictive value of CCE-1 reported in the studies. The sensitivity of CCE-2 was found to be comparable to the sensitivity of colonoscopy, although its specificity was slightly low. There was no retrievable evidence on mortality rate, survival rate and quality of life and quality adjusted life years gained related to screening CRC using capsule endoscopy in general population.

8.2 SAFETY

There was fair level of evidence to show that both CCE-1 and CCE-2 were safe to be used in the screening for colorectal cancer among the average and increased risk patients. Most of the adverse events were mild and related to bowel preparation. Both types of capsule endoscopy claimed to have received CE mark, with CCE-2 received US FDA approval to be used in cases of failed or incomplete colonoscopy.

8.3 COST EFFECTIVENESS

There was limited evidence on cost-effectiveness of CCE-1 in screening for CRC. In the Markov model, a hypothetical population of 100,000 individuals aged 50 years and over who underwent a 10 yearly screening procedure, the incremental cost–effectiveness (compared with no screening) of colonoscopy and capsule endoscopy was $16,165 and $29,244 per life–year saved, respectively. With 30% increase in compliance to screening, CCE-1 became more cost-effective than colonoscopy. However, there was no retrievable evidence on economic evaluation conducted on CCE-2.

8.4. COMPETING TECHNOLOGIES

There was insufficient retrievable evidence that assessed virtual endoscopy such as CTC in comparison with capsule endoscopy particularly in the general population screening.

8.5. ORGANIZATIONAL ISSUES

Level of accuracy of capsule endoscopy depends on the adequacy of bowel preparation and the experience of the readers. Spada et al. and Van Gossum et al. found that sensitivity of CCE was significantly higher in the patients with good or excellent cleanliness as compared with the patients with poor or fair cleanliness.Sidhu et al. found that the interpretation of CCE images was largely dependent on the expertise and experience of the gastroenterologist. Jang et al. also showed that the inter-observer differences were greatest for subtle lesions which were often missed by trainees and that experience with conventional endoscopy is important in reviewing CCE findings. Hence, proper and continuous training of staff is essential especially in reading and interpreting CCE images.

Good acceptability and higher uptake of capsule endoscopy was found among average and increased risk of CRC patients. Groth et al. found that offering capsule endoscopy led to a fourfold increase of screening uptake compared to standard colonoscopy while Pilz et al. found that patients preferred capsule endoscopy to colonoscopy. Capsule endoscopy was also found to be feasible and easily performed as an out-of-clinic procedure according to a study done by Adler et al.

Triantafyllou et. al and Pioche et. al found that capsule endoscopy performed after colonoscopy failure or in those contraindicated for colonoscopy is feasible and safe. Hence, in individuals at high risk and contraindicated for conventional colonoscopy, or those who are unwilling to undergo colonoscopy, capsule endoscopy could provide an alternative to conventional colonoscopy.

9 RECOMMENDATION

The accuracy of CCE-1 was found to be suboptimal as compared to colonoscopy. There were wide variations in the sensitivity, specificity, positive predictive value and negative predictive value of CCE-1 reported in the studies. The sensitivity of CCE-2 was found to be comparable to the sensitivity of colonoscopy although the specificity was slightly low. There was no retrievable evidence on mortality rate, survival rate and quality of life related to screening CRC using capsule endoscopy in the general population.

Based on this review, CCE-2 may be considered as a diagnostic tool to identify colonic polyps or CRC among patients with average or increased risk of CRC, particularly among those who are unwilling to undergo colonoscopy, have contraindication for colonoscopy and have history of incomplete colonoscopy.

However, for general population screening for CRC, capsule endoscopy cannot be recommended yet until further quality evidence is available.

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Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

HIERARCHY OF EVIDENCE FOR TEST ACCURACY STUDIES

Level Description

1. A blind comparison with reference standard among an appropriate sample of consecutive patients

2. Any one of the following
3. Any two of the following
4. Any three or more of the following

- Narrow population spectrum
- Differential use of reference standard
- Reference standard not blind
- Case control study

5. Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

Appendix 3

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL CAPSULE ENDOSCOPY FOR COLORECTAL CANCER (CRC) SCREENING

1 BACKGROUND INFORMATION

Colorectal cancer (CRC) is a malignant tumour arising within the walls of the large intestine, including the segments in the caecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum. Majority of cases begin as non-cancerous (benign) polyps, which slowly increases in size, followed by dysplasia and finally developed into cancer. Risk of developing CRC depends on many factors, including age, smoking, diet and genetic inheritance with family history of CRC, hereditary nonpolyposis, or familial adenomatous polyposis.

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008. In a systematic review and meta-analysis of 8 studies, Spada et al. reported that the overall prevalence of polyps of any size and significant findings at colonoscopy was 57% (399 cases) and 27.4% (221 cases), respectively. In Malaysia, colorectal cancer (CRC) is the second most common cancer among men and women with a total of 2,246 cases diagnosed in 2007 reported to National Cancer Registry (NCR), which represent 12.3 % of all cases reported. The incidence of CRC in 2007 was slightly higher among males with age-standardised rate (ASR) of 13.4 per 100,000 population compared to females (ASR 10.2 per 100,000 population). The incidence was highest among Chinese where the ASR for males and females were 19.4 and 14.6 per 100,000 populations respectively.

CRC is a largely preventable disease which requires community participation in the prevention process, such as life style modification and regular medical screening. Screening for CRC offers the best hope for early detection of preclinical or early symptomatic and improved survival. Good evidence suggests that screening reduces mortality from colorectal cancer by up to 53%. Several methods are currently available for colorectal cancer screening which include fecal occult blood test (FOBT), immunochemical fecal occult blood test (iFOBT), stool DNA test, colonoscopy, barium enema, flexible sigmoidoscopy and computed tomography (CT) colonography.

Conventional colonoscopy is suggested to be the optimal technique to be used for CRC screening programs in high-risk population, allowing a 90% decrease in CRC incidence. It is the only method with the ability to remove detected polyps and obtain biopsy specimens. However, no more than 25% of compliance has been achieved in the screening programmes due to the drawbacks of conventional colonoscopy, such as being painful, patient's embarrassment or the need for sedation. Participation in any method of colorectal cancer screening among average risk individuals in Malaysia was found to be extremely low (0.7%).The main barriers identified from this study were feeling of embarrassment, being busy, not bothered and fear of finding out.

Therefore, there is a need for an additional safe, minimally invasive method for visualizing the colon that might serve as an additional screening method for the early detection of colorectal cancer and adenomatous polyps. On the basis of the technological development and the previous clinical experiences with the small bowel capsule endoscope, the colon capsule endoscope (CE) is claimed to offer an alternative noninvasive technique that allows exploration of the colon without requiring sedation and air insufflations. In 2006, Given Imaging Ltd. developed the first generation of capsule (CCE-1) specifically designed for colon visualisation. A second-generation colon capsule (CCE-2) was later developed to increase the sensitivity for detection of colonic findings and to simplify the procedure.

Capsule endoscopy (CE) is a disposable, small, wireless, ingestible capsule, equipped with an endoscope which allows a direct visualisation of the gastrointestinal mucosa. It requires the use of a colon capsule, data recorder and computer software for video processing and viewing. The envelope of the capsule is made of biocompatible materials, sealed with biocompatible adhesives. The first generation capsule endoscopy measures 31 by 11 mm and has two imagers that enable it to acquire video images from both ends. The angle of view from each imager is 156°. It has a total operating time of 10 hours and acquires images at a rate of 4 frames per second (2 for each imager) when virtually stationary and 35 images per second when in motion. The advanced system of capsule image rate is a result from bidirectional communication between the capsule and the data recorder. The recorder consists of an antenna array that is attached to the patient's abdomen, a receiver, and memory for data storage during the examination. After completion of the examination, the recorder is connected to a workstation for downloading the images, processing and subsequent viewing. Dedicated computer software includes tools for video processing, polyp size estimation and a virtual chromoendoscopy system. At the beginning of the examination, CE turns on and transmits images for 3 min before it enters a "sleep" mode for 1 hour and 45 minutes to save battery energy. After this time, it automatically switches on and reactivates in the terminal ileum, allowing a complete colonic exploration.

The second generation of colon capsule endoscopy is similar to the first generation CE and consists of a slightly bigger, ingestible video capsule. The angle of view has been increased to 172 degrees. In particular, the frame rate has been increased from 4 to 35 images per second to adequately image the mucosa when the capsule is accelerated by peristalsis. Prior to either CE procedures, the patient adheres to a bowel preparation regimen specifically designed for the CE procedure. Similar to colonoscopy, a clean colon is achieved by the consumption of a clear liquid diet and 4 L of polyethylene glycol in a split-dose fashion prior to colon capsule ingestion. With CE, however, the bowel preparation is also required to help promote capsule propulsion distally through the bowel, as the colon has only a few spontaneous longitudinal contractions per day. For this reason, adding one or two doses of sodium phosphate (NaP) helps to accelerate colon capsule transit through both the small and large bowel within the operating time of the capsule battery.

With the significant burden of CRC in Malaysia, The National Cancer Control Blueprint which was approved and endorsed by the Cabinet in November 2008 stated that screening for CRC should be initiated and implemented. Capsule endoscopy is a new technology with evolving indication for CRC screening. Therefore, a Health Technology Assessment (HTA) is required to assess the diagnostic accuracy, safety, effectiveness and cost-effectiveness of capsule endoscopy for CRC screening in adult population.

This HTA was requested by the Head of Clinical Research Centre, Sultanah Bahiyah Hospital, Alor Setar, Kedah who is also the National Advisor of the Gastroenterology Services.

2 POLICY QUESTION

Should capsule endoscopy be used to screen adult population for colorectal cancer?

3 OBJECTIVES

3.1 To determine the diagnostic accuracy of capsule endoscopy for CRC screening in adult population compared with conventional colonoscopy.
3.2 To assess the safety of capsule endoscopy compared with conventional colonoscopy in CRC screening.
3.3 To determine the benefits of CRC screening using capsule endoscopy compared with conventional colonoscopy, with regards to patient outcomes such as detection rate, cancer mortality rate, survival rate, quality of life and quality adjusted life years (QALY) gained.
3.4 To determine the economic impacts of using capsule endoscopy compared with conventional colonoscopy for CRC screening.
3.5 To assess the ethical, legal, and organisational aspects related to CRC screening using capsule endoscopy.

Research Questions

i. How accurate is capsule endoscopy compared to conventional colonoscopy in CRC screening?
ii. How safe is capsule endoscopy compared with conventional colonoscopy in CRC screening?
iii. What are the short term and long term benefits of using capsule endoscopy compared with conventional colonoscopy for CRC screening?
iv. What are the economic implications of using capsule endoscopy compared with conventional colonoscopy for CRC screening?
v. What are the ethical, legal, and organizational issues related to CRC screening using capsule endoscopy?

4 METHODOLOGY

4.1. SEARCH STRATEGY

Electronic database will be searched for published literatures pertaining to capsule endoscopy for CRC screening.

4.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the bibliographies of the related articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 The search strategy will be included in the appendix

4.2 INCLUSION AND EXCLUSION CRITERIA

4.2.1 Inclusion criteria

a. Population : Adults, aged more than 18 years old

b. Intervention : Capsule endoscopy

c. Comparators : Conventional colonoscopy

d. Outcome :
i. Polyp detection rate, adenoma detection rate, cancer detection rate, any pathology (e.g. diverticula) detected, mortality rate, survival rate, quality of life, and quality adjusted life years (QALY) gained.
ii. Diagnostic accuracy: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of capsule endoscopy.
iii. Adverse events related to the use capsule endoscopy as a CRC screening test.
iv. Cost, cost-benefit, cost-effectiveness, and cost utility of using capsule endoscopy for CRC screening.

e. Study design : HTA reports, systematic review, randomised controlled trial (RCT), diagnostic accuracy studies, cross-sectional, cohort, case-control, and economic evaluation studies

f. Publication : Full text articles

4.2.2 EXCLUSION CRITERIA

i. Hereditary colorectal cancer
ii. Animal study
iii. Narrative review
iv. Laboratory study

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 DATA EXTRACTION STRATEGY

The following data will be extracted:

4.3.1 Details of methods and study population characteristics
4.3.2 Details of intervention and comparators
4.3.3 Details of individual outcomes for effectiveness, safety and cost associated with capsule endoscopy for CRC screening
4.3.4 Details on diagnostic accuracy (sensitivity, specificity, PPV, NPV) of screening test/tests used in CRC screening

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion.

4.4 QUALITY ASSESSMENT STRATEGY

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP).

4.5 METHODS OF ANALYSIS / SYNTHESIS

Data on the diagnostic accuracy, effectiveness, safety and cost-effectiveness of capsule endoscopy for CRC screening will be presented in tabulated format with narrative summaries. No meta-analysis will be conducted for this Health Technology Assessment.

5 REPORT WRITING

APPENDIX 4

SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and Ovid MEDLINE® 1948 to present

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
4. (colorectal adj1 (carcinoma* or tum?r or cancer* or neoplas*)).tw.
5. COLONIC POLYPS/
6. (polyp* adj1 colonic).tw.
7. ADENOMATOUS POLYPS/
8. (adenomatous adj1 polyp*).tw.
9. RECTAL NEOPLASMS/
10. (tumor* adj1 rectal).tw.
11. ((rectal or rectum) adj1 neoplasm*).tw.
12. ((rectal or rectum) adj1 cancer*).tw.
13. (((colorectal or colon or colonic or sigmoid or rectal or rectum or anus or anal or bowel) adj2 neoplasm*) or cancer* or carcinoma* or tumo?r*).tw.
14. Colorectal tumour.tw.
15. bowel cancer.tw.
16. CRC.tw.
17. mass screening.tw.
18. early detection of cancer/
19. screening/
20. screening.mp.
21. mass screening/
22. mass screening.tw.
23. screening.tw.
24. early detection of cancer.mp.
25. early detection of cancer.tw.
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
27. CAPSULE ENDOSCOPY/
28. (endoscop* adj1 (capsule or wireless capsule or video capsule)).tw.
29. (capsule endoscop* adj1 (video or wireless)).tw.
30. colon capsule endoscopy.tw.
31. PillCam.tw.
32. PCCE.tw.
33. PCC-1.tw.
34. PCC-2.tw.
35. CCE-1.tw.
36. CCE-2.tw.
37. Video capsule endoscopy.tw.
38. Wireless capsule endoscopy.tw.
39. COLONOSCOPY/
40. colonoscop*.tw.
41. (colonoscopic adj1 (surger* or surgical procedure)).tw.
42. Optical colonoscopy.tw.
43. white light endoscopy.tw.
44. WLE.tw.

45. Immunologic Tests/ or Immunochemistry/f?ecal immunochemical test$.tw.
46. (Immunochemical adj (f?ecal occult blood test$ or faeces test$ or stool test$ or FOBT$1)).tw.
47. (immunologic$ adj (f?ecal occult blood test$ or FOB test$ or FOB$1 or test$)).tw.
48. (automatic immunochemical f?ecal occult blood test$ or automated immunochemical FOBT or immune f?ecal occult blood test$).tw.
49. (IFOBT$1 or I-FOBT$1 or auto iFOBT or qFIT or LA-FOBT or Quantitative iFOBT's or Hemosure IFOBT or CFOBT or SFOBT).tw.
50. (F?ecal DNA test$ or F?ecal DNA or fluorescence long DNA test$ or FL-DNA test Stool-based deoxyribonucleic acid test$ or L-DNA).tw.
51. Sigmoidoscopy/ or flexible sigmoidoscopy.mp.
52. (sigmoidoscop* adj3 (surgical or procedure*)).tw.
53. (sigmoidoscop* adj1 surger*).tw.
54. sigmoidoscop*.tw.
55. proctosigmoidoscop*.tw.
56. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57. 26 and 56

Ovid- EBM Reviews- Cochrane Central Register of Controlled Trials (November 2014)

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
4. (colorectal adj1 (carcinoma* or tum?r or cancer* or neoplas*)).tw.
5. COLONIC POLYPS/
6. (polyp* adj1 colonic).tw.
7. ADENOMATOUS POLYPS/
8. (adenomatous adj1 polyp*).tw.
9. RECTAL NEOPLASMS/
10. (tumor* adj1 rectal).tw.
11. ((rectal or rectum) adj1 neoplasm*).tw.
12. ((rectal or rectum) adj1 cancer*).tw.
13. (((colorectal or colon or colonic or sigmoid or rectal or rectum or anus or anal or bowel) adj2 neoplasm*) or cancer* or carcinoma* or tumo?r*).tw.
14. Colorectal tumour.tw.
15. bowel cancer.tw.
16. CRC.tw.
17. mass screening.tw.
18. early detection of cancer/
19. screening/
20. screening.mp.
21. mass screening/
22. mass screening.tw.
23. screening.tw.
24. early detection of cancer.mp.
25. early detection of cancer.tw.
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
27. CAPSULE ENDOSCOPY/
28. (endoscop* adj1 (capsule or wireless capsule or video capsule)).tw.
29. (capsule endoscop* adj1 (video or wireless)).tw.
30. colon capsule endoscopy.tw.

31. PillCam.tw.
32. PCCE.tw.
33. PCC-1.tw.
34. PCC-2.tw.
35. CCE-1.tw.
36. CCE-2.tw.
37. Video capsule endoscopy.tw.
38. Wireless capsule endoscopy.tw.
39. COLONOSCOPY/
40. colonoscop*.tw.
41. (colonoscopic adj1 (surger* or surgical procedure)).tw.
42. Optical colonoscopy.tw.
43. white light endoscopy.tw.
44. WLE.tw.
45. Immunologic Tests/ or Immunochemistry/f?ecal immunochemical test$.tw.
46. (Immunochemical adj (f?ecal occult blood test$ or faeces test$ or stool test$ or FOBT$1)).tw.
47. (immunologic$ adj (f?ecal occult blood test$ or FOB test$ or FOB$1 or test$)).tw.
48. (automatic immunochemical f?ecal occult blood test$ or automated immunochemical FOBT or immune f?ecal occult blood test$).tw.
49. (IFOBT$1 or I-FOBT$1 or auto iFOBT or qFIT or LA-FOBT or Quantitative iFOBT's or Hemosure IFOBT or CFOBT or SFOBT).tw.
50. (F?ecal DNA test$ or F?ecal DNA or fluorescence long DNA test$ or FL-DNA test Stool-based deoxyribonucleic acid test$ or L-DNA).tw.
51. Sigmoidoscopy/ or flexible sigmoidoscopy.mp.
52. (sigmoidoscop* adj3 (surgical or procedure*)).tw.
53. (sigmoidoscop* adj1 surger*).tw.
54. sigmoidoscop*.tw.
55. proctosigmoidoscop*.tw.
56. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57. 26 and 56

Ovid- EBM Reviews- Cochrane Database of Systematic Reviews (2005 to October 2014)

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
4. (colorectal adj1 (carcinoma* or tum?r or cancer* or neoplas*)).tw.
5. COLONIC POLYPS/
6. (polyp* adj1 colonic).tw.
7. ADENOMATOUS POLYPS/
8. (adenomatous adj1 polyp*).tw.
9. RECTAL NEOPLASMS/
10. (tumor* adj1 rectal).tw.
11. ((rectal or rectum) adj1 neoplasm*).tw.
12. ((rectal or rectum) adj1 cancer*).tw.
13. (((colorectal or colon or colonic or sigmoid or rectal or rectum or anus or anal or bowel) adj2 neoplasm*) or cancer* or carcinoma* or tumo?r*).tw.
14. Colorectal tumour.tw.
15. bowel cancer.tw.
16. CRC.tw.
17. mass screening.tw.

18. early detection of cancer/
19. screening/
20. screening.mp.
21. mass screening/
22. mass screening.tw.
23. screening.tw.
24. early detection of cancer.mp.
25. early detection of cancer.tw.
26. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
27. CAPSULE ENDOSCOPY/
28. (endoscop* adj1 (capsule or wireless capsule or video capsule)).tw.
29. (capsule endoscop* adj1 (video or wireless)).tw.
30. colon capsule endoscopy.tw.
31. PillCam.tw.
32. PCCE.tw.
33. PCC-1.tw.
34. PCC-2.tw.
35. CCE-1.tw.
36. CCE-2.tw.
37. Video capsule endoscopy.tw.
38. Wireless capsule endoscopy.tw.
39. COLONOSCOPY/
40. colonoscop*.tw.
41. (colonoscopic adj1 (surger* or surgical procedure)).tw.
42. Optical colonoscopy.tw.
43. white light endoscopy.tw.
44. WLE.tw.
45. Immunologic Tests/ or Immunochemistry/f?ecal immunochemical test$.tw.
46. (Immunochemical adj (f?ecal occult blood test$ or faeces test$ or stool test$ or FOBT$1)).tw.
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57. 26 and 56

Ovid- EBM Reviews- Database of Abstracts of Review of Effects (4th Quarter 2014)

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
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5. COLONIC POLYPS/
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51. Sigmoidoscopy/ or flexible sigmoidoscopy.mp.
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53. (sigmoidoscop* adj1 surger*).tw.

54. sigmoidoscop*.tw.
55. proctosigmoidoscop*.tw.
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57. 26 and 56

Ovid- EBM Reviews- Health Technology Assessment (4th Quarter 2014)

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
4. (colorectal adj1 (carcinoma* or tum?r or cancer* or neoplas*)).tw.
5. COLONIC POLYPS/
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7. ADENOMATOUS POLYPS/
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57. 26 and 56

Ovid- EBM Reviews-NHS Economic Evaluation Database (4th[t] Quarter 2014)

1. COLONIC NEOPLASMS/
2. ((cancer* or neoplasm*) adj1 colon*).tw.
3. COLORECTAL NEOPLASMS/
4. (colorectal adj1 (carcinoma* or tum?r or cancer* or neoplas*)).tw.
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57. 26 and 56

Pubmed Search terms

((((((((("Colonic Neoplasms"[Mesh]) OR ((((((((((Neoplasm* Colonic[Title/Abstract]) OR Colonic Neoplasm[Title/Abstract]) OR Colon Neoplasm*[Title/Abstract]) OR Neoplasm* Colon[Title/Abstract]) OR Cancer of Colon[Title/Abstract]) OR Cancer of the Colon[Title/Abstract]) OR Colon Cancer*[Title/Abstract]) OR Cancer* Colon[Title/Abstract]) OR Colonic Cancer*[Title/Abstract]) OR Cancer* Colonic[Title/Abstract]) OR Colon tumour[Title/Abstract]) OR Colorectal cancer[Title/Abstract])) OR "Colorectal Neoplasms, Hereditary Nonpolyposis"[Mesh]) OR ((((((((((Hereditary Nonpolyposis[Title/Abstract]) OR Colorectal Neoplasm*[Title/Abstract]) OR Familial Nonpolyposis Colon Cancer[Title/Abstract]) OR Colon Cancer Familial Nonpolyposis[Title/Abstract]) OR Hereditary Nonpolyposis Colorectal Cancer[Title/Abstract]) OR Colorectal Cancer Hereditary Nonpolyposis[Title/Abstract]) OR Hereditary Nonpolyposis Colon Cancer[Title/Abstract]) OR Lynch Syndrome I[Title/Abstract]) OR Lynch Cancer Family Syndrome I[Title/Abstract]) OR Lynch Syndrome[Title/Abstract]) OR Syndrome Lynch[Title/Abstract])) OR "Colonic Polyps"[Mesh]) OR ((Colonic Polyp*[Title/Abstract]) OR Polyp* Colonic[Title/Abstract])) OR "Adenomatous Polyps"[Mesh]) OR ((Adenomatous Polyp*[Title/Abstract]) OR Polyp* Adenomatous[Title/Abstract]))) AND (("Capsule Endoscopy"[Mesh]) OR ((((((((((((Capsule Endoscop*[Title/Abstract]) OR Endoscop* Capsule[Title/Abstract]) OR Wireless Capsule Endoscop*[Title/Abstract]) OR Capsule Endoscop* Wireless[Title/Abstract]) OR Endoscop* Wireless Capsule[Title/Abstract]) OR Video Capsule Endoscop*[Title/Abstract]) OR Capsule Endoscop* Video[Title/Abstract]) OR Endoscop* Video Capsule[Title/Abstract]) OR PillCam[Title/Abstract]) OR PCCE[Title/Abstract]) OR PCC-1[Title/Abstract]) OR PCC-2[Title/Abstract]) OR CCE-1[Title/Abstract]) OR CCE-2[Title/Abstract]))) OR (("Colonoscopy"[Mesh]) OR (((((((((Colonoscop*[Title/Abstract]) OR Colonoscopic Surgical Procedure*[Title/Abstract]) OR Procedure* Colonoscopic Surgical[Title/Abstract]) OR Surgical Procedure* Colonoscopic[Title/Abstract]) OR Surger* Colonoscopic[Title/Abstract]) OR Colonoscopic Surger*[Title/Abstract]) OR Optical colonoscopy[Title/Abstract]) OR white light endoscopy[Title/Abstract]) OR WLE[Title/Abstract])) Filters: Humans

Appendix 5

CASP CHECKLIST

SYSTEMATIC REVIEW

CRITERIA ASSESSED			
Selection of studies (relevant studies included?)	Yes	No	Can't tell
Assessment of quality of included studies?	Yes	No	Can't tell
If the results of the review have been combined, is it reasonable to do so? (heterogeneity)	Yes	No	Can't tell

ECONOMIC EVALUATION

CRITERIA ASSESSED			
A well-define question posed?	Yes	No	Can't tell
Comprehensive description of competing alternative given?	Yes	No	Can't tell
Effectiveness established?	Yes	No	Can't tell
Effects of intervention identified, measured and valued appropriately?	Yes	No	Can't tell
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	Yes	No	Can't tell
Costs and consequences adjusted for different times at which they occurred (discounting)?	Yes	No	Can't tell
Results of the evaluation?	Yes	No	Can't tell
Incremental analysis of the consequences and costs of alternatives performed?	Yes	No	Can't tell
Sensitivity analysis performed?	Yes	No	Can't tell

Appendix 6

FIRST GENERATION CAPSULE ENDOSCOPY (CCE-1)

Evidence Table : **EFFICACY/EFFECTIVENESS**
Question : **Is first generation capsule endoscopy effective for screening adult population for colorectal cancer?**

Bibliographic citation	1. Spada C, Hassan C, Marmo R et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clin Gastroenterol Hepatol 2010; 8: 516–522
Study type/Method	Meta-analysis **Objective** To assess the accuracy of CCE in detecting colorectal polyps. The MEDLINE, EMBASE, and SCOPUS databases were searched, from 2006 to 2009, for the terms “colon capsule” and “Pillcam colon”; searches included abstracts. Methods of the analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews of Meta-Analyses (PRISMA) recommendations. The risk of bias within each study was ascertained according to Quality Assessment of Diagnostic Accuracy in Systematic Reviews recommendations. The risk of bias across studies was assessed using the interstudy heterogeneity statistic, meta-regression, and the Egger test (2-sided p<0.1 is significant). The primary end point (1) per-patient sensitivity and specificity of CCE for polyps of any size (2) per-patient sensitivity and specificity of CCE for significant findings The secondary end point 1) per-patient sensitivity of CCE for CRC (2)rate of capsule excretion (3) level of excellent-good bowel preparation for CCE (4) CCE safety profile CCE accuracy was defined by a per-patient analysis to emphasize the impact of CCE in a clinical and screening setting rather than the technical ability of CCE to find colonic lesions. Per-patient sensitivity and specificity were calculated for polyps of any size and for significant findings (polyps, ≥6 mm in size or >3 in number). Forest plots were produced based on random-effect models.
LE	1
Number of patients & Patient characteristics	Eight studies were included in the meta-analysis, provided data on 837 patients • Eliakim et al 2006 • Schoofs et al 2006 • Van Gossum et al. 2009 • Sieg et al. 2009 • Spada et al. 2008 • Gay et al. 2009 • Sacher-Huvelin et al. 2009 • Pilz et al. 2008 A total of 837 patients enrolled; • median age, 57.5 y; range, 54–60 y • male sex, 57%; range, 37%–83%) **Inclusion criteria** • subjects at average or increased risk of CRC • underwent CCE and complete colonoscopy for verification 31 (3.7%) patients were excluded from the final analysis **Exclusion criteria** • Studies without details of polyps and their verification with colonoscopy • those with fewer than 10 patients, review articles, position papers, editorials, commentaries, or book chapters.

Intervention	PillCam® Colon 1 (CCE-1)
Comparison	
Length of follow up	
Outcome measures / Effect size	High levels of heterogeneity (interstudy heterogeneity, ≥75%) were not detected. Moderate heterogeneity partially was explained by the different design of individual studies. **Primary end point** • Prevalences of polyps and significant findings were 57% and 27.4%, respectively. • CCE sensitivity and specificity for polyps of any size were 71% (95% CI, 66%–76%) and 75% (95% CI, 66%–83%), respectively. I^2 = 12.9% and 53.4 % for sensitivity and specificity, respectively Moderate heterogeneity (specificity) due to 1 screening study in which low prevalence may have favoured high specificity reportings. .• Capsule excretion rate - CCE overall excretion rate was 86% (95% CI, 83%–88%). • level of excellent-good bowel preparation for CCE The median of the rates of an excellent-good level was 77%, ranging between 27% and 89% among the different series • CCE safety profile - Side effects were reported by 7 series. - Overall, 29 cases occurred in 701 patients, corresponding to a rate of 4.1% (95% CI, 2.6%–5.6%). - All the side effects were mild/moderate (ie, nausea, abdominal pain), with the exception of one case of postpolypectomy peritonitis caused by the operative colonoscopy rather than to CCE examination. **Risk of bias across studies** • Funnel plot does not show a meaningful asymmetry • Egger test was not significant (p=0.3 for polyp any size, p=0.8 for significant study) **Author's conclusion** • CCE sensitivity for polyps and significant findings compares favourably with other non-invasive or less-invasive colorectal cancer screening strategies. • CCE specificity is likely to be underestimated because reference colonoscopy examination results are blinded. • CCE estimates of accuracy should not be projected immediately in a screening setting because most of the included studies included disease enriched populations.
General comments	

Bibliographic citation	2. Rokkas T, Papaxoinis K, Triantafyllou K, Ladas, SD. A meta-analysis evaluating the accuracy of colon capsule endoscopy in detecting colon polyps. Gastrointest Endosc 2010;71:792-798
Study type/Method	Meta-analysis **Objective** To meta-analyze the data of existing CCE trials to determine the yield and miss rate of CCE. **Data sources** Studies that estimated the accuracy of CCE were identified. Extensive English-language, computer-aided medical literature searches of the PubMed/MEDLINE and Embase databases for human studies were performed **Search terms used:** colon and capsule and endoscopy or wireless endoscopy. Two authors extracted data from each study independently by using a predefined form, and disagreements were resolved by discussion and consensus by a third reviewer. The fixed-effects or random-effects model was used as appropriate, based on whether homogeneity or heterogeneity, respectively, was indicated by the Cochran Q test. **Main Outcome Measurements:** Per-patient sensitivity and specificity, with 95% confidence intervals (CI). Findings were categorized as "significant polyps," = polyp ≥6 mm in size or 3 or more polyps of any size "any polyp," = any polyp found, independent of size.
LE	I
Number of patients & Patient characteristics	A total of 7 studies (total of 626 individuals) were included i. Schoofs et al.2006 ii. Eliakim et al. 2006 iii. Lewis et al. 2006 iv. Van Gossum et al. 2009 v. Sieg et al., 2009 vi. Sacher-Huvelin et al., 2009 vii. Costamagna et al., 2009 **Inclusion criteria:** (1) written in the English language (2) providing sufficient data for the authors to construct a 2 x 2 contingency table to calculate sensitivity and specificity.
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	**Accuracy** For pooled data (random effects analysis); • For any polyp found, per-patient CCE sensitivity of 73% (95% CI, 68%-77%) and specificity of 89% (95% CI, 81%-94%). - Heterogeneity in sensitivities was not observed among the studies (Cochran Q test =0.81, df = 3, P=0.85, I^2= 0%). - Specificities were heterogeneous (Q test =18.6, df =3, P =0 .0003, I^2 = 83.9%). - The AUC under the sROC (weighted symmetric summary receiver operating curve) was 0.7965. • For significant polyps, per-patient CCE sensitivity and specificity were 69% (95% CI, 62%-75%) and 86% (95% CI, 82%-90%). - Heterogeneity in sensitivities was not observed - among the studies (Cochran Q test = 2.76, df = 5, p =0.74,I^2= 0%). - Specificities were heterogeneous (Q test =0. 32, df = 5, p =0 .000, I^2 = 84.4%). - The AUC for the sROC was 0.7886. **Capsule excretion rate** Capsules were expelled within 10 hours after ingestion in 85.3% (95% CI; 66.3-94.5) of the individuals. **Author's conclusion** CCE is a reasonable method for screening asymptomatic individuals for colorectal polyps. It may be particularly useful for patients with "incomplete" colonoscopy, those with contraindications for conventional colonoscopy, and those unwilling to undergo colonoscopy because of its perceived inconvenience and discomfort.
General comments	

Bibliographic citation	3.Medical Advisory Secretariat. Capsule Endoscopy for Colorectal Cancer Screening: an evidence-based analysis. Ontario Health Technology Assessment Series 2009;9(9)
Study type/Method	HTA, Meta-analysis **Objective** • To determine accuracy of capsule endoscopy in the detection of CRCs and polyps in individuals 50 years of age and older, compared with the gold standard of optical colonoscopy • Safety of capsule endoscopy procedure **Method of Review** • Studies meeting inclusion criteria were selected from the database of search results. • Data on the study characteristics, patient characteristics, primary and secondary outcomes, and adverse events were abstracted. **Inclusion Criteria** Prospective studies comparing accuracy of capsule endoscopy with optical colonoscopy in detection of colorectal cancers and polyps **Statistical Methods** • A meta-analysis of diagnostic yield using Review Manager (RevMan 4.1) software • The incremental yield (IY) was calculated by subtracting the yield of colonoscopy from that of PillCam Colon, and a 95% CI was determined. • A fixed-effect model was applied if there was no heterogeneity, and a random effect model (DerSimonian-Laird) was applied if there was heterogeneity in reported sensitivities between the studies. **Outcome Measures** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of capsule endoscopy for detection of colorectal cancers and polyps compared with the reference standard colonoscopy. Incremental yield (IY) (yield of capsule endoscopy minus yield of colonoscopy) and 95% confidence interval for detection of colorectal cancers and polyps, using fixed-effect model
LE	
Number of patients & Patient characteristics	Included 2 studies: i. Eliakim et al. 2006 ii. Schoofs et al. 2006
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	No study heterogeneity was identified across the two studies. **Accuracy** • For the detection of significant polyps (defined as >6 mm or ≥3 polyps), the pooled sensitivity was 73% (54%–87%) and pooled specificity was 92% (84%–97%). • For the detection of 'any polyp', CCE had a 57% yield compared with 61% yield for colonoscopy [IY, –0.05 (95% CI; –0.18 to 0.07), p = 0.4 -Heterogeneity: Chi^2 = 0.03, df = 1 (p = 0.85), I^2 = 0% • For detection of significant polyps, CCE had a 31% yield compared with a 29% yield for colonoscopy with a IY of 0.05 (95% CI; –0.14 to 0.24, p = 0.6 -Heterogeneity: Chi^2 = 2.48, df = 1 (p = 0.12), I^2 = 59.7% **Capsule excretion**: within 10 hours in 70% of the patients who received a single booster oral sodium phosphate and in 78% of those who received a second dose. **Safety profile** No adverse events were related to the capsule procedures and that all patients tolerated the colon-preparation regimen. **Author's conclusion** • CCE is a non-invasive method for identifying colorectal polyps. It has, however, lower sensitivity and specificity than colonoscopy • There were no significant differences in the yield of CCE and colonoscopy.
General comments	Funding: Ontario Ministry of Health and Long Term Care, Canada

Bibliographic citation	4. Sacher-Huvelin S. Coron E. Planche L. Benamcuzing R. Maunoury V. Filoche B. Frederic M. Saurin J-C. Subtile C. Lecleire S. Cellier C. Coumaros D. Heresbach D. Galmiche J.P. Colon capsule endoscopy vs colonoscopy in patients at average or increased risk of colorectal cancer. *Aliment Pharmacol Ther* 2010; 32: 1145–1153
Study type/Method	• Prospective, multicentre trial • This study was conducted prospectively from April 2007 to July 2009 in each 16 French academic centres which fulfill the patient criteria. • Patients at average or increased risk of CRC were enrolled in each centre • CCE was performed on day 1 and continue with colonoscopy on day 2. • In each centre, one to three experienced endoscopists performed all colonoscopies, while capsule videos were interpreted separately by one single independent endoscopist per centre. CCEs and colonoscopies were performed by endoscopists, unaware of each other's findings.
LE	I
Number of patients & Patient characteristics	545 paticipant were selected **Inclusion criteria:** (i)healthy, asymptomatic individuals 50–74 years old who accept colonoscopy in the context of a screening programme (average risk group) (ii) asymptomatic patients with a personal or family history of CRC or polyps, but without colonoscopy during the preceding 3 years (increased risk group). **Exclusion criteria** (i) the presence of dysphagia (ii) symptoms suggestive of intestinal obstruction (iii) recently complicated colonic diverticulosis (iv) advanced heart or kidney failure (v) the presence of a cardiac pace-maker or other implanted electro-medical device (vi) pregnancy
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	

Length of follow up	
Outcome measures / Effect size	**Prevalence and accuracy of detection of polyps** • Overall, colonoscopy detected more patients with polyps than did CCE. • 311 (57%) patients had polyps of any size detected by colonoscopy compared with 249 seen at CCE (46%; p < 0.0001). • Polyps ≥6 mm and ≥10 mm, the corresponding figures were 112 (21%) vs. 94 (17%) (p = 0.097) and 43 (8%) vs. 29 (5%) (p = 0.03) respectively. • Five patients with CRC were detected by colonoscopy compared with only three detected by CCE. The two missed cancers were located in the sigmoid colon and rectum, and both were relatively large tumours (35 mm and 15 mm respectively). • For the 545 patients, the CCE accuracy of detection of polyps ≥6 mm or CRC was 39% (95% CI; 30–48) for sensitivity, 88% (95% CI; 85–91) for specificity, 47% (95% CI; 37–57) for the positive predictive value (PPV) and 85% (95% CI; 82–88) for the negative predictive value (NPV). • The non-inferiority between CCE and colonoscopy for the detection of polyps ≥6 mm was not acceptable either for sensitivity [absolute difference 51% (95% CI; −58; −43)] or for NPV [absolute difference −13% (95% CI; −16; −10)]. • For 118 patients, the results of CCE and colonoscopy were discordant concerning the primary criterion of judgement. All of the CCE videos of these discordant cases were reviewed by the expert panel. This reinterpretation of the capsule videos improved the diagnostic yield of CCE, with sensitivity increasing to 57% (95% CI; 48–66), specificity to 95% (95% CI; 93–97), PPV to 73% (95% CI; 63–82) and NPV to 90% (95% CI; 87–92). • For advanced adenomas, the sensitivity of CCE was better, at 72%, and an NPV of 94%. • Overall, the results were almost the same in the screening and surveillance cohorts and in the intention-to-diagnose and per-protocol cohorts. **Bowel cleanliness**: CCE accuracy was better in the group of patients with good or excellent cleanliness compared with those with poor or fair preparation. -In the well-prepared patients, the NPV increased to 88% (95% CI; 83–92) for polyps ≥6 mm and 98% (95% CI; 96–99) for polyps ≥10 mm, but sensitivity remained low [53% (95% CI; 39–67) for polyps ≥6 mm]. **Safety and tolerability** -Nineteen adverse events were reported. -Most of these were of mild or moderate severity -Only three severe adverse events occurred, which were either potentially related to bowel preparation. -No severe adverse event was related to the capsule itself. -comparison of VAS scores showed a slight (probably not clinically relevant) statistical difference in favour of CCE compared with colonoscopy (8.74 ± 1.56 vs. 8.25 ± 2.00; p < 0.0001). **Conclusion** Although well-tolerated, CCE cannot replace colonoscopy as a first line investigation for screening and surveillance of patients at risk of cancer.
General comments	Funding: French Ministry of Health, University Hospital of Nantes, Given Imaging Ltd

Bibliographic citation	5.Herrerias Gutiérrez J.M., Argüelles-Arias F. Cunedo-Álvarez A. San- Juan-A costa M., Romero-Vázquez, Garc a-Montes J.M., Pellicer-Bautista F. PillCam © Colon Capsule for the study of colonic pathology in clinical practice. Study of agreement with colonoscopy. Rev Esp Enferm Dig 2011; 103 (2): 69-75
Study type/Method	Diagnostic accuracy Study **Objective** to assess accuracy, the agreement in the diagnosis of CCE with conventional colonoscopy The physician performing the capsule procedure and reading the capsule and the physician performing the conventional colonoscopy study were blinded for the other technique
LE	2
Number of patients & Patient characteristics	A total of 144 subjects were included in the study (67 women and 77 men) Mean age ± SD= 52.17±16.71 years ***Patient indication:*** • screening of colorectal cancer (88 patient) • control after polypectomy (24) • incomplete colonoscopy (7) • rectal bleeding (10) • anaemia (8) • diarrhoea (7) In 44 cases a colonoscopy was carried out after CCE. The rest of patients (100 patient) refused conventional colonoscopy
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	• The exploration with CCE was completed in 134/144 cases (93%), without any case of retention. • The colonic finding in 134 CCE were : -34 cases - no lesions -diverticulosis in 63 cases -polyps in 43 cases -angiodysplasia 15 cases -Crohn's disease in 9 cases -ulcerative colitis in 8 cases • Compared to colonoscopy, the rate of agreement was 75.6% • The sensitivity was 84% and the specificity was 62.5%, PPV was 77.7% and NPV was 71.4% • In 4 cases CCE was positive with negative colonoscopy. Two cases were diverticulosis and 2 had one angiodysplasia that was not seen by colonoscopy • Concerning detection of polyps, CCE detect 19 polyps (two of them not detected by colonoscopy) and colonoscopy detected 19 polyps (two of them not detected by CCE) **Bowel preparation** was good in 88/134 (65,6%) fair in 26/134 (19.4%) and poor in 20/134 (15%) of the cases. The average colonic transit was 140.76 min (9-603). No adverse effect was notified.
General comments	

Bibliographic citation	6. Pilz J.B. Portmann S., Peter S. Beglinger C. Degen L. Colon Capsule Endoscopy compared to Conventional Colonoscopy under routine screening. BMC Gastroenterol 2010; 10: 66
Study type/Method	Prospective, single-center pilot study **Objective** to evaluate CCE method for performance as a screening tool compared to colonoscopy in asymptomatic patients under routine screening conditions. Patients underwent CCE (Pillcam) on day 1 and colonoscopy on day 2. The examinations were carried out by different physicians, with blinding of results until both examinations had been completed and until interobserver evaluation was finished. Adverse events were recorded on days 1 and 2 of the study. **The primary endpoint** the number of cancerous lesions and polyps detected on CCE compared to colonoscopy. **Secondary endpoints** completeness of the exam, patient acceptance and adherence to preparation regimen. Subanalyses regarding effect of bowel preparation on polyp detection on CCE and accuracy of detection with respect to histopathology were performed.
LE	3
Number of patients & Patient characteristics	A total of 59 patients were enrolled in this study. 3 patients excluded from the data analysis because the capsule did not reach the colon during examination time A total of 56 patients (34 male, 22 female) participate in this study -mean age 60 years, median 59 years, range 38-84 years, (86% 50 years or older) Patient characteristic: - age of 50 years without symptoms or with lower gastrointestinal signs and symptoms - individuals younger than 50 years with positive family history for CRC, minimum 18 years were included in this study Patient exclusion: - CRC in the patient's history -cardiac pacemaker, -contraindications for sodium phosphate solution -risk factors for capsule retention including surgical intestinal anastomosis, Crohn's Disease, diverticulitis and radiologically suspected bowel obstruction.
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd

Comparison	
Length of follow up	2007-2008
Outcome measures/ Effect size	**Polyp detection** • Polyp detection rate (per-patient) was 50% (n = 28) for colonoscopy and 62% (n = 35) for CCE. • Significant size polyps were diagnosed in 6 patients (11%) on colonoscopy, 15 patients (27%) on CCE. • 11% (n = 6) patients had polyps of any size on colonoscopy that were not detected on CCE. 13/56 (23%) patients had findings of any size on CCE that were not verified on colonoscopy, 2 (4%) were of significant size. • For polyps of any size, CCE showed a sensitivity of 79% (95% CI; 61 to 90), specificity 54% (95% CI; 35 to 70), PPV of 63% and NPV of 71% for polyps of any size. • For overall polyp size, detection of polyps on CCE and on colonoscopy was independent with statistical significance (p = 0.013), indicating differences in the detection rate for polyps on both examinations • For relevant polyps (>5 mm) there was a correspondence in the detection rates of both methods (p > 0.05). The sensitivity was 50% (95% CI; 19 to 81), the specificity was 76% (95% CI; 63 to 86), the PPV was 20% and the NPV was 93% **Histopathology** • Per-patient-prevalence of adenoma was 27% (n = 15) on colonoscopy. • Numbers are too small to calculate for sensitivity and specificity, but all (n = 3) of the detected tubulo-villous adenoma were detected by CCE. • Tubular adenoma were detected in 18% (a total of 10 patients on colonoscopy, all size), one the two detected tubular adenoma of significant size on colonoscopy was classified as ≤5 mm on CCE. • One of the two detected serrated adenoma was not seen on CCE. • No high-grade dysplasia or cancerous lesion was found on either type of examination. • Overall prevalence of hyperplastic polyps was 23% (n = 13). **Adverse events** • One patient had an allergic skin reaction to the adhesive tape of the electrodes during CCE. • One patient presented with abdominal pain after polypectomy (during colonoscopy). **Patients' acceptance** • No patient reported troubles swallowing the capsule. • 16 patients (30%) felt restricted during daily-life activities by carrying the electrodes and the recorder. • 21 (40%) patients preferred CCE to colonoscopy, while 20 (38%) preferred colonoscopy and 12 (23%) had no preference. • 50 (94%) patients would recommend CCE. • 44 (83%) subjects would prefer to undergo a capsule colonoscopy again in ten years' time for screening purposes compared to 8 patients (15%) who declined and 1 patient (2%) who was indecisive. **Conclusion** • CCE provides a screening solution which is minimally invasive, safe and does not require sedation. • It is an easy to perform examination with an excellent NPV for application in screening purposes under routine conditions. However, diagnostic accuracy for relevant size polyps (i.e. sensitivity) is low.
General comments	Funding: University Hospital Basel, Given Imaging Ltd

Evidence Table : SAFETY
Question : Is first generation capsule endoscopy safe for screening adult population for colorectal cancer?

Bibliographic citation	1. Spada C, Hassan C, Marmo R et al. Meta-analysis shows colon capsule endoscopy is effective in detecting colorectal polyps. Clin Gastroenterol Hepatol 2010; 8: 516–522
Study type/Method	Meta-analysis **Objective** To assess the accuracy of CCE in detecting colorectal polyps. The primary end point (1) per-patient sensitivity and specificity of CCE for polyps of any size (2) per-patient sensitivity and specificity of CCE for significant findings The secondary end point 1) per-patient sensitivity of CCE for CRC (2)rate of capsule excretion (3) level of excellent-good bowel preparation for CCE (4) CCE safety profile
LE	I
Number of patients & Patient characteristics	Eight studies were included in the meta-analysis, provided data on 837 patients • Eliakim et al. 2006 • Schoofs et al. 2006 • Van Gossum et al. 2009 • Sieg et al. 2009 • Spada et al. 2008 • Gay et al. 2009 • Sacher-Huvelin et al. 2009 • Pilz et al. 2008 A total of 837 patients enrolled; • median age, 57.5 y; range, 54–60 y • male sex, 57%; range, 37%–83%)
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	CCE safety profile - Side effects were reported by 7 series. • Overall, 29 cases occurred in 701 patients, correspondingto a rate of 4.1% (95% CI; 2.6%–5.6%). • All the side effects were mild/moderate (ie, nausea, abdominal pain), with the exception of one case of postpolypectomy peritonitis caused by the operative colonoscopyrather than to CCE examination.
General comments	

Bibliographic citation	2. Sacher-Huvelin S. Coron E. Planche L. Benamcuzing R. Maunoury V. Filoche B. Frederic M. Saurin J-C. Subtile C. Lecleire S. Cellier C. Coumaros D. Heresbach D. Galmiche J.P. Colon capsule endoscopy vs colonoscopy in patients at average or increased risk of colorectal cancer. Aliment Pharmacol Ther 2010; 32: 1145–1153
Study type/Method	Prospective, multicentre trial This study was conducted prospectively from April 2007 to July 2009 in each 16 French academic centres which fulfill the patient criteria. Patients at average or increased risk of CRC were enrolled in each centre CCE was performed on day 1 and continue with colonoscopy on day 2. In each centre, one to three experienced endoscopists performed all colonoscopies, while capsule videos were interpreted separately by one single independent endoscopist per centre. CCEs and colonoscopies were performed by endoscopists, unaware of each other's findings.
LE	I
Number of patients & Patient characteristics	545 paticipant were selected **Inclusion criteria:** (i) healthy, asymptomatic individuals 50–74 years old who accept colonoscopy in the context of a screening programme (average risk group) (ii) asymptomatic patients with a personal or family history of CRC or polyps, but without colonoscopy during the preceding 3 years (increased risk group). **Exclusion criteria** (i) the presence of dysphagia (ii) symptoms suggestive of intestinal obstruction (iii) recently complicated colonic diverticulosis (iv) advanced heart or kidney failure (v) the presence of a cardiac pace-maker or other implanted electro-medical device (vi) pregnancy
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	**Safety and tolerability** -Nineteen adverse events were reported. -Most of these were of mild or moderate severity -Only three severe adverse events occurred, which were either potentially related to bowel preparation. -No severe adverse event was related to the capsule itself. -comparison of VAS scores showed a slight (probably not clinically relevant) statistical difference in favour of CCE compared with colonoscopy (8.74 ± 1.56 vs. 8.25 ± 2.00; $p < 0.0001$).
General comments	

Bibliographic citation	3.Pilz J.B. Portmann S., Peter S. Beglinger C. Degen L. Colon Capsule Endoscopy compared to Conventional Colonoscopy under routine screening. *BMC Gastroenterol* 2010; 10: 66
Study type/Method	Prospective, single-center pilot study **Objective** to evaluate CCE method for performance as a screening tool compared to colonoscopy in asymptomatic patients under routine screening conditions. Patients underwent CCE (Pillcam) on day 1 and colonoscopy on day 2. The examinations were carried out by different physicians, with blinding of results until both examinations had been completed and until interobserver evaluation was finished. Adverse events were recorded on days 1 and 2 of the study. **The primary endpoint** the number of cancerous lesions and polyps detected on CCE compared to colonoscopy. **Secondary endpoints** completeness of the exam, patient acceptance and adherence to preparation regimen. Subanalyses regarding effect of bowel preparation on polyp detection on CCE and accuracy of detection with respect to histopathology were performed.
LE	3
Number of patients & Patient characteristics	A total of 59 patients were enrolled in this study. 3 patients excluded from the data analysis because the capsule did not reach the colon during examination time A total of 56 patients (34 male, 22 female) participate in this study - mean age 60 years, median 59 years, range 38-84 years, (86% 50 years or older) **Patient characteristic:** - age of 50 years without symptoms or with lower gastrointestinal signs and symptoms - individuals younger than 50 years with positive family history for CRC, minimum 18 years were included in this study **Patient exclusion:** - CRC in the patient's history - cardiac pacemaker, - contraindications for sodium phosphate solution - risk factors for capsule retention including surgical intestinal anastomosis, Crohn's Disease, diverticulitis and radiologically suspected bowel obstruction.
Intervention	PillCam® Colon 1 (CCE-1)Given Imaging Ltd
Comparison	
Length of follow up	2007-2008
Outcome measures/ Effect size	**Adverse events** • One patient had an allergic skin reaction to the adhesive tape of the electrodes during CCE. • One patient presented with abdominal pain after polypectomy (during colonoscopy).
General comments	

Bibliographic citation	4 Triantafyllou K, Viazis N, Tsibouris P, Zacharakis G, Kalantzis C, Karamanolis DG, Ladas SD. Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further workup in clinical practice. Gastrointest Endosc. 2014;79:307–316.
Study type/Method	Prospective, follow-up study. Setting: Three tertiary-care centers. **Objective:** To investigate the extent that CCE complements incomplete colonoscopy and guides further workup Patients underwent CCE either immediately after colonoscopy or were rescheduled. Further investigations were guided by the results of CCE
LE	II-3
Number of patients & Patient characteristics	75 outpatients 39 had a screening colonoscopy. Patients: Consecutive outpatients after colonoscopy failure
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	
Length of follow up	2 years
Outcome measures / Effect size	**Safety profile** 10% of patients reported mild adverse events (AE).
General comments	

Evidence Table : COST EFFECTIVENESS
Question : Is first generation capsule endoscopy cost-effective in screening adult population for colorectal cancer?

Bibliographic citation	1. Hassan C, Zullo A, Winn S et al. Cost-effectiveness of capsule endoscopy in screening for colorectal cancer. Endoscopy. 2008;40(5):414-421
Study type/Method	Cost effectiveness analysis (CEA) **Objective** to provide a model to assess the cost and effectiveness of population–based screening for colorectal cancer (CRC) using capsule endoscopy and to compare the cost–effectiveness with that of a colonoscopy screening program CEA by a computer model based on a Markov process. **Perspective**: Societal **Time Horizon**: Life-time The effectiveness data were derived from the published literature. The estimates for the base-case analysis were selected in consultation with a principal investigator and an expert panel. The main clinical parameters included the transition probabilities for the different health states, the sensitivity and specificity of the two screening strategies for different sizes of polyps and CRC, and the screening-related complication rates. The principal health states in the model: • no colorectal neoplasia • diminutive (≤5mm), medium(6-9mm) size or large (≥10mm) adenomatous polyp • localised,regional or distant CRC • CRC related death **Incremental cost-effectiveness ratio (ICER)** between 2 strategies, including no screening = difference in cost/ difference in life expectancy (cost per life-year gained). **ICER threshold** USD 100,000 per life-year gained • Estimated cost for CCE and reading time USD 950 • Indirect cost for colonoscopy and capsule endoscopy estimated based on median hourly income rate USD 18.62/hour **Discounted** at an annual rate of 3%. One- and two-way **sensitivity analyses** were used
LE	I
Number of patients & Patient characteristics	A hypothetical population of 100 000 individuals aged 50 years and over, undergoes a 10 yearly screening procedure.
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd

Comparison	No screening Colonoscopy Every 10 years
Length of follow up	
Outcome measures/ Effect size	• When compared with no screening, both resulted in decrease of CRC-related costs • Colonoscopy reduced CRC-related costs by 71%,but high cost of screening, follow-up tests, treatment of screening related complications • At baseline, the incremental cost–effectiveness (compared with no screening) of colonoscopy and capsule endoscopy was $16,165 and $ 29,244 per life–year saved, respectively. • When equal compliance was simulated, the colonoscopy program was more effective and less costly than capsule endoscopy based strategy • When simulating an initial compliance to capsule endoscopy 30% better than colonoscopy, capsule endoscopy became the more effective and more cost–effective option. • A 20% better compliance was sufficient when a higher accuracy of capsule endoscopy for polyps was assumed • Capsule endoscopy with a 6mm threshold for postcapsule colonoscopy referral resulted in 8,927 discounted LYS, without a 6mm threshold resulted in 8,255 LYS, and colonoscopy resulted in 10,669 LYS. • Capsule endoscopy with a 6mm threshold for postcapsule colonoscopy referral resulted in costs of $465 million, without a 6mm threshold resulted in $412 million, and colonoscopy resulted in $377 million. **Author's conclusion** The most influential parameters were the accuracy of capsule endoscopy and the compliance rate, especially in relation to the more invasive colonoscopy. The cost-effectiveness of capsule endoscopy depends mainly on its ability to improve compliance to CRC screening.
General comments	

SECOND GENERATION CAPSULE ENDOSCOPY (CCE-2)

Evidence Table : **EFFICACY/EFFECTIVENESS**
Question : **Is second generation capsule endoscopy effective in screening adult population for colorectal cancer?**

Bibliographic citation	1. Spada C, Hassan C, Munoz-Navas M et al. Second-generation colon capsule endoscopy compared with colonoscopy *Gastrointest Endosc* 2011; 74(5) : 1174
Study type/Method	Prospective, multicenter trial including 8 European sites. **Objective** To assess the feasibility, accuracy, and safety of CCE-2 in comparison with colonoscopy Colonoscopy was independently performed (blinded to the results of CCE-2) within 10 hours after capsule ingestion or on the next day. No unblinding of colon capsule endoscopy results at colonoscopy was carried out. **Outcomes** • CCE-2 sensitivity and specificity for detecting patients with polyps ≥6 mm and ≥10 mm, • Capsule excretion rate • level of bowel preparation • rate of adverse events Patients without endoscopically confirmed polyps ≥6 mm or ≥10 mm were classified as having a negative result at the reference standard (standard colonoscopy). Capsule-positive but colonoscopy-negative cases were counted as false positive.
LE	2
Number of patients & Patient characteristics	117 patients recruited Mean age ± SD = 60 ± 9 years 72 men Patients at average or increased risk of colorectal neoplasia Data from 109 patients were analyzed. Eight of 117 patients (6.8%) were excluded from the efficacy analysis: • inability to swallow the capsule (1 case) • technical failure of the data recorder (2 cases) • capsule technical failure (2 cases). • capsule remained in the cecum during the entire procedure (2 cases) • Withdrawal from study (1 case)
Intervention	PillCam Colon 2 (CCE-2) Given Imaging Ltd

Comparison	
Length of follow up	
Outcome measures / Effect size	At colonoscopy, a total of 45 patients (41.3%) had at least one polyp ≥6 mm. Thirty-two patients (29.3%) had at least one polyp that was ≥10 mm. **Accuracy** • Overall polyp detection rate (regardless of size) at colonoscopy and CCE-2 was 84% and 81%, respectively. • Per-patient CCE-2 sensitivity for polyps ≥6 mm and ≥10 mm was 84% and 88%, with specificities of 64% and 95%, respectively • 39 (36%) and 30 (28%) patients were seen with at least one adenoma ≥6 mm and ≥10 mm, respectively. CCE-2 correctly classified 35 and 28 of these patients, corresponding to a detection rate for ≥6 mm and ≥10 mm neoplasia of 90% (95% CI; 80%-99%) and 93% (95% CI; 84%-100%), respectively. All 3 invasive carcinomas were detected by CCE-2. • In 7 false-negative cases at CCE-2, a size mismatch (ie, measured as <6 mm at CCE-2) occurred in 3 patients, with a polyp ≥6 mm at colonoscopy (6-9 mm, 2 cases; ≥10 mm, 1 case), whereas 4 were actually missed by CCE-2, later identified by re-reading as polyps • CCE-2 identified diverticulosis and erythema/ inflammation in 24 and 4 patient respectively. Colonoscopy detected these in 32 and 11 patients, respectively. CCE-2 detected diverticulosis and erythema/inflammation that were not diagnosed by colonoscopy in an additional 27 and 7 patients, respectively. **Capsule excretion rate** was 88% within 10 hours. **Colon cleanliness** for CCE-2 was adequate in 81% of patients **Adverse events** • 8 out of 117(6.8%) mild to moderate adverse events were reported which resolved spontaneously within 24 to 48 hours. - 5 were related to bowel preparation and included vomiting, nausea, and abdominal pain. - 2 experienced fatigue because of the long capsule procedure. - 1 patient experienced severe adverse event not related to colon capsule endoscopy: colon perforation after polypectomy. **Author's Conclusion:** CCE-2 appeared to have a high sensitivity for the detection of clinically relevant polypoid lesions, and it might be considered an adequate tool for colorectal imaging.
General comments	Authors are speakers for Given Imaging Ltd.

Bibliographic citation	2. Eliakim R, Yassin K, Niv Y et al. Evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy 2009; 41: 1026–1031
Study type/Method	Feasibility study, in 5 centres Second-generation capsule endoscopy was prospectively compared with conventional colonoscopy as gold standard for the detection of colorectal polyps and other colonic disease, in a cohort of patients scheduled for colonoscopy and having known or suspected colonic disease. **Objective** • To determine the performance of the second-generation PillCam Colon 2 capsule endoscopy system compared with conventional colonoscopy for the detection of patients with colonic polyps and other colonic disease. • The capsule was ingested in the morning and conventional colonoscopy, which was the gold standard, was carried out after capsule egestion or up to 10 hours post capsule ingestion, whichever came first, on the same day. • Colonoscopy was independently performed within 10 hours after capsule ingestion. • Capsule-positive but colonoscopy-negative cases were counted as false-positive. • Adverse events were recorded prospectively, on the day of the procedure by interviewing the patient and a week later by a follow-up telephone call. Events were graded as mild, moderate, or severe by the investigator specifically assigned for each patient. • Per-patient capsule sensitivity and specificity for polyp detection versus colonoscopy were calculated according to polyp size with a 95% confidence interval (CI),in which colonoscopy was considered to be a gold standard.
LE	2
Number of patients & Patient characteristics	104 patients (mean age 49.8 years)
Intervention	PillCam Colon 2 (CCE2) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	• 44% of patients had polyps of any size, 53% of these patients had adenomas. • CCE-2 detected polyps of any size in 45 patients (46% of patients); of these,35 (36% of patients) had polyps ≥ 6mm including 17 patients(17% of patients) with polyps ≥ 10 mm. • In addition to polyps, CCE-2 detected other disease. CCE-2 detected diverticulosis in 9 patients and erythema/inflammation in 7 (78 %) and 3 (75 %) of these patients respectively. • The capsule sensitivity for the detection of patients with polyps ≥ 6mm was 89% (95% confidence interval [CI] 70–97) and for those with polyps ≥ 10mm it was 88% (95% CI; 56–98) • CCE-2 specificities for the detection of patients with polyps ≥ 6mm and with polyps ≥ 10mm were 76% (95% CI; 72–78) and 89% (95% CI; 86–90), respectively. Overall **colon cleanliness** for capsule endoscopy was adequate in 78% of patients (95 % CI; 68–86). Overall eight **adverse events** (8 %) were reported in seven patients. -No adverse events were reported that directly related to capsule or colonoscopy procedures. -7 were related to the preparation: five were mild-moderate headaches/nausea which resolved within 24 hours and two were mild vomiting which resolved within 48 hours. -One patient had urinary retention, rated as a severe adverse event unrelated to the study.
General comments	Funding: Given Imaging Ltd.

Bibliographic citation	3. Hagel A.F. Gabele E. Raithel M. et al. Colon capsule endoscopy: Detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies. Can J Gastroenterol Hepatol. 2014 Feb;28(2):77-82.
Study type/Method	Diagnostic Study Patients who were scheduled to undergo colonoscopy for known or suspected colonic diseases were included in the present study. CCE (Pillcam Colon 2) was performed first, followed by colonoscopy the day after.The recorded CCE videos were interpreted by two investigators who are highly experienced with SB capsule endoscopy and specifically trained for CCE. Colonoscopy was performed by experienced endoscopists in all cases. The colonoscopists were blinded to the capsule reader's results. In case of a CCE-reported finding missed during colonoscopy, the endoscopist was unblinded with respect to this finding only. All data calculated and statistically analyse **The primary end point:** -the accuracy of CCE versus colonoscopy in identifying colorectal polyps. -For this per-finding analysis, polyps were divided into three subgroups according to their size (<6 mm, 6 mm to 9 mm and ≥10 mm) or location (right, transverse, left colon). Polyps in CCE with corresponding polyps regarding size and/or location in colonoscopy were classified as true positive. Cases with no polyps at CCE and colonoscopy were classified as true negative. If CCE detected a polyp with no corresponding polyp at colonoscopy, this finding was classified as false positive for CCE. If colonoscopy detected a polyp that was not reported by CCE, this finding was classified as false negative for CCE. **Secondary end point:** -a per-patient analysis was conducted to evaluate the accuracy of PillCam Colon 2 in identifying patients with any colonic polyps whatsoever.
LE	3
Number of patients & Patient characteristics	In total, 24 patients (14 male, 10 female) with an average age of 51 years (range 24 to 75 years) were included in the present study. However, 23 of 24 were completed the examination; one examination was terminated in the transverse colon due to unmanageable pain in the patient. Seven (29%) patients had undergone polypectomy in the past, five (22%) had a positive family history for CRC, eight (33%) underwent endoscopy for screening purposes, two (8%) experienced diarrhoea for more than two weeks and two (8%) were scheduled for surveillance colonoscopy due to known ulcerative colitis **Inclusion criteria** -Indications for CRC screening, -personal or family history of CRC or adenomatous polyps, with no previous colonoscopy within three years. **Exclusion criteria** -swallowing disorders -congestive heart failure, -contraindication for the laxatives used in the study, -pregnancy -implanted cardiac devices.
Intervention	PillCam Colon 2 (CCE-2) Given Imaging Ltd
Comparison	

Length of follow up	
Outcome measures / Effect size	CCE accuracy for detecting polyps (per-finding analysis): • In 6 of 23 cases, both colonoscopy and CCE did not detect polyps (true negative). In the other 17 cases, 47 polyps were detected. Forty of 47 (85.1%) polyps were apparent in both examinations (true positive). Locations were: cecum (n=3), ascending (n=6), transverse (n=9), descending (n=8), sigmoid colon (n=10) and rectum (n=4). • 4 (8.5%) polyps were detected by colonoscopy but missed at CCE (false negative). These polyps had a size of 6 mm to 12 mm and were located in the transverse colon and the cecum. • 3 (6.4%) polyps were detected by CCE: size 3 mm and 7 mm, and 11 mm in the cecum or the ascending colon but not recon-firmed at colonoscopy (false positive). One of these three polyps (3 mm) was located in the cecum and could not be identified by colonoscopy even after unblinding of the endoscopist for this finding. However, three of the latter seven polyps were recorded in patients who had more than one polyp, which were all detected by both methods. • According to this per-finding analysis, CCE achieved an overall sensitivity of 90.9% (95% CI; 85% to 100%) and a specificity of 67.6% (95% CI; 36% to 98%) in the detection of any size polyp. Compared with colonoscopy, polyps were found by CCE with a PPV and NPV of 93.0% and 71.4%, respectively. CCE accuracy for identifying patients as polyp carriers (per-patient analysis): • At colonoscopy, a total of 16 of 23 (69.6%) patients had ≥1 polyp of any size. At least one polyp was identified by CCE in 14 of 23 (60.8%) patients. In 13 (56.5%) patients, CCE-positive patients were recon-firmed by colonoscopy (true positive). In six (26.1%) patients, CCE and colonoscopy detected no polyp (true negative). In a single CCE-positive patient (4.3%) no polyp was recorded at colonoscopy (false positive). In three (13.1%) CCE-negative patients, colonoscopy identified at least one polyp (false negative). • According to these data, in the per-patient analysis, CCE could identify patients with polyps regardless of the number or size with a sensitivity of 81.5% (95% CI; 62% to 100%) and a specificity of 85.7% (95% CI; 60% to 100%). The PPV of CCE with respect to identifying patients with colorectal polyps was 92.9%; the NPV was 67%. **Nonpolyp colonic findings** -CCE detected additional colonic lesions such as an angiodysplasia in the ascending colon, diverticulae in four patients (17%) and a severe inflammation due to ulcerative colitis in one patient each (4%). **Extracolonic findings** *Oesophagus* -Pathological findings, such as oesophagitis (I°: n=4, IV°: n=1), suspected Barrett's oesophagus (COM1 according to the Prague classification) and varices (I° according to Sarin's classification) due to portal hypertension, were recorded in seven of 24 patients (29%). *Gastric* -In nine of 24 (38%) patients, pathological findings, such as mucosal erythema, erosions and portal hypertensive gastropathy, were recorded. *Small Bowel* -In 14 of 24 (58%) patients, pathological findings, such as angiodysplasias, erosions, ulcerations, strictures, diverticula orifices or polyps, were recorded **Adverse events** -One patient reported headache during preparation for the CCE procedure. -No other adverse events were recorded during the CCE and colonoscopy.
General comments	

Evidence Table : **SAFETY**
Question : **Is second generation capsule endoscopy safe in screening adult population for colorectal cancer?**

Bibliographic citation	1. Spada C, Hassan C, Munoz-Navas M et al. Second-generationcolon capsule endoscopy compared with colonoscopy *Gastrointest Endosc* 2011; 74(5): 1174
Study type/Method	Prospective, multicenter trial including 8 European sites. **Objective** To assess the feasibility, accuracy, and safety of CCE-2 in comparison with colonoscopy Colonoscopy was independently performed (blinded to the results of CCE-2) within 10 hours after capsule ingestion or on the next day.No unblinding of colon capsule endoscopy results at colonoscopy was carried out. **Outcomes** • CCE-2 sensitivity and specificity for detecting patients with polyps ≥6 mm and ≥10 mm, • Capsule excretion rate • level of bowel preparation • rate of adverse events
LE	2
Number of patients & Patient characteristics	117 patients recruited Mean age ± SD = 60 ± 9 years 72 men Patients at average or increased risk of colorectal neoplasia Data from 109 patients were analyzed. Eight of 117 patients (6.8%) were excluded from the efficacy analysis: • inability to swallow the capsule (1 case) • technical failure of the data recorder (2 cases) • capsule technical failure (2 cases). • capsule remained in the cecum during the entire procedure (2 cases) • Withdrawal from study (1 case)
Intervention	PillCam Colon 2 (CCE-2) Given Imaging Ltd
Comparison	Colonoscopy
Length of follow up	
Outcome measures / Effect size	**Adverse events** • 8 out of 117(6.8%) mild to moderate adverse events were reported which resolved spontaneously within 24 to 48 hours. - 5 were related to bowel preparation and included vomiting, nausea, and abdominal pain. - 2 experienced fatigue because of the long capsule procedure. - 1 patient experienced severe adverse event not related to colon capsule endoscopy: colon perforation after polypectomy.
General comments	

Bibliographic citation	2. Eliakim R, Yassin K, Niv Y et al. Evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy 2009; 41: 1026–1031
Study type/Method	Feasibility study, in 5 centres Second-generation capsule endoscopy was prospectively compared with conventional colonoscopy as gold standard for the detection of colorectal polyps and other colonic disease, in a cohort of patients scheduled for colonoscopy and having known or suspected colonic disease. **Objective** • To determine the performance of the second-generation PillCam Colon 2 capsule endoscopy system compared with conventional colonoscopy for the detection of patients with colonic polyps and other colonic disease. • Adverse events were recorded prospectively, on the day of the procedure by interviewing the patient and a week later by a follow-up telephone call. Events were graded as mild, moderate, or severe by the investigator specifically assigned for each patient.
LE	2
Number of patients & Patient characteristics	104 patients (mean age 49.8 years)
Intervention	PillCam Colon 2 (CCE2) Given Imaging Ltd
Comparison	Colonoscopy
Length of follow up	
Outcome measures / Effect size	Overall eight **adverse events** (8 %) were reported in seven patients. -No adverse events were reported that directly related to capsule or colonoscopy procedures. -7 were related to the preparation: five were mild-moderate headaches/nausea which resolved within 24 hours and two were mild vomiting which resolved within 48 hours. -One patient had urinary retention, rated as a severe adverse event unrelated to the study.
General comments	

Bibliographic citation	3. Hagel A.F. Gabele E. Raithel M. et al. Colon capsule endoscopy: Detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies. Can J Gastroenterol Hepatol. 2014 Feb;28(2):77-82.
Study type/Method	**Diagnostic Study** Patients who were scheduled to undergo colonoscopy for known or suspected colonic diseases were included in the present study. CCE (Pillcam Colon 2) was performed first, followed by colonoscopy the day after.The recorded CCE videos were interpreted by two investigators who are highly experienced with SB capsule endoscopy and specifically trained for CCE. Colonoscopy was performed by experienced endoscopists in all cases. The Colonoscopists were blinded to the capsule reader's results. In case of a CCE-reported finding missed during colonoscopy, the endoscopist was unblinded with respect to this finding only. All data calculated and statistically analyse **Primary end point:** the accuracy of CCE versus colonoscopy in identifying colorectal polyps. **Secondary end point:** a per-patient analysis was conducted to evaluate the accuracy of PillCam Colon 2 in identifying patients with any colonic polyps whatsoever
LE	3
Number of patients & Patient characteristics	In total, 24 patients (14 male, 10 female) with an average age of 51 years (range 24 to 75 years) were included in the present study. However, 23 of 24 were completed the examination; one examination was terminated in the transverse colon due to unmanageable pain in the patient. Seven (29%) patients had undergone polypectomy in the past, five (22%) had a positive family history for CRC, eight (33%) underwent endoscopy for screening purposes, two (8%) experienced diarrhea for more than two weeks and two (8%) were scheduled for surveillance colonoscopy due to known ulcerative colitis **Patient characteristic** **Inclusion criteria** -Indications for CRC screening, -personal or family history of CRC or adenomatous polyps, with no previous colonoscopy within three years. **Exclusion criteria** -swallowing disorders -congestive heart failure, -contraindication for the laxatives used in the study, -pregnancy -implanted cardiac devices.
Intervention	PillCam Colon 2 (CCE2) Given Imaging Ltd
Comparison	Colonoscopy
Length of follow up	
Outcome measures / Effect size	**Adverse events** -One patient reported headache during preparation for the CCE procedure. -No other adverse events were recorded during the CCE and the colonoscopy endoscopies.
General comments	

Organizational

Bibliographic citation	1. Groth S. Krause H. Behrendt R. Hill H. Börner M. Bastürk M. Plathner N. Schütte F Gauger U. Reimann J. F. Altenhofen L. And Rösch T. Capsule colonoscopy increases uptake of colorectal cancer screening. *BMC Gastroenterol* 12:80
Study type/Method	Prospective study • Objective: to evaluate the uptake of CCE as an alternative to colonoscopy when offered to insured person for screening. • 2150 letters mailed to insured persons insured, who were over 55 years of age and eligible for CRC screening • Of those, 154 persons contacted one of the 4 gastroenterologists named in the letter and presented for a personal interview. After this discussion and reading the standardized informed consent, persons decided to undergo either colonoscopy or capsule. The **main outcome** parameter • The potential increase in the rate of persons accepting conventional or capsule colonoscopy among all persons invited compared with the mean annual uptake of colonoscopy in the preceding 3 years • A significant difference in uptake, for a one-sided comparison, would be reached at an increased uptake of 1.6% versus 1% (p = 0.045), and for a two-sided comparison at 1.7% (p = 0.049) **Secondary outcome parameters** *were* • Adenoma yield • Rate of capsule examinations with sufficient bowel preparation • Adverse events and complications • Patient opinion and acceptability
LE	3
Number of patients & Patient characteristics	154 patients 88 men, 66 women Mean age 63.3 years, (colonoscopy group) 62.7 (capsule group) **Inclusion criteria** -age > 55 years -No previous colonoscopy in last 10 years -eligible for CRC screening 7 were excluded - not eligible for screening 124 decided to undergo either colonoscopy (n = 34) or capsule (n = 90), while 23 finally opted against both forms of endoscopic screening. The percentage of men was higher in the capsule group (64.4% vs. 47.1% for colonoscopy)
Intervention	PillCam® Colon 1 (CCE-1) Given Imaging Ltd
Comparison	

Length of follow up	
Outcome measures / Effect size	**Primary outcome:** **General acceptance and uptake** • the uptake of any endoscopic screening test (capsule or conventional colonoscopy) stimulated by the project invitation letters was 5.8 % (124/2150), with 34 (1.6 %) opting for primary colonoscopy and 90 (4.2 %) choosing primary capsule endoscopy. • Comparing these rates to the spontaneous rate set at 1 %, the increase was 60 % for colonoscopy (1.6 % versus 1 %, p = 0.075; two sided comparison) and more than 4 fold (4.2 % versus 1 %; p < 0.001) for capsule colonoscopy. • Regarding sex distribution, uptake was 5.6 % in men and 2.8 % in women (p = 0.002). **Secondary outcome:** • **Bowel cleanliness** was graded excellent in none, good in 28, moderate in 45 and poor in 11 cases (12.2 %). - Incomplete colonic capsule passage was found in 15/89 cases, and in 7 of those the rectum was reached. - In one case spontaneous passage through the colon occurred before the capsule was activated. - full colonic visualization on the basis of complete capsule passage was possible in 73/89 cases (82 %). • **Adenoma yield** - 9 patients with 13 low-grade adenomas (all <1 cm) were found in the colonoscopy group. This accounts for a patient rate with at least one adenoma of 26.4 % (CI; 12.9 %, 44.4 %) and an adenoma rate (all adenomas/all patients) of 38.2 % (CI; 22.2 %, 56.4 %); this difference was statistically significant (p = 0.018, Fisher exact tests, two sided). - 16 patients underwent colonoscopy because of positive capsule findings suggesting polyps; in addition, 6/15 with incomplete capsule endoscopy followed the recommendation to undergo colonoscopy. Of these 22 patients overall, 8 cases were identified who had a total of 14 adenomas (of those, 5 were 1 cm or greater) in the capsule group. - In summary, the patient rate with at least one adenoma for capsule colonoscopy, based on secondary colonoscopy results, was 9 % (8/90; CI; 4.7 %, 18.1 %), and the adenoma rate (all adenomas/all cases) was 15.5 % (CI; 8.8 %, 24.7 %). Also this difference was statistically significant (p = 0.013, Fisher exact tests, two sided) **Adverse events** -no reported adverse events in any of the study participants. **Patient opinion and acceptability** • Amongst those persons who eventually underwent one of the two tests, the main reason for a final choice of capsule was the fear of colonoscopy-related discomfort and complications, while the main reason for choosing colonoscopy was the possibility for taking tissue samples and carrying out polypectomy. • Among participants in the capsule group who were asked whether capsule colonoscopy would be again the method of choice for repeated colonic examination, 65 % answered “yes” and 22 % “probably yes”, after capsule colonoscopy. The corresponding values for colonoscopy were 94 % and 0 %. • 22 persons who underwent colonoscopy after capsule, 16 answered the questionnaire and 11 stated they would choose conventional colonoscopy for a repeat examination, mainly because everything could be done in one procedure and colonoscopy was felt to be more accurate. Two further persons said that they would probably choose capsule rather than conventional colonoscopy. **Conclusion** Uptake of colorectal screening can be increased by offering capsule endoscopy in addition to colonoscopy. However, capsule endoscopy sensitivity needs to be improved.
General comments	Funding: BKK-24 Medical Insurance

Bibliographic citation	2. 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): 559-567
Study type/Method	Prospective, single center study **Objective:** To assess the feasibility, accuracy and acceptability of CCE-2 in detection of significant lesions in colorectal cancer risk patients, unable or unwilling to perform colonoscopy. In all patients the readers were instructed to review the entire CCE examination using Rapid 7 software and additionally to note significant extra-colonic findings. CCE procedure completion rate, level of bowel preparation and rate of adverse events were assessed. **End points** A new end point of "positive" examination: the diagnostic utility index (findings directly explaining symptoms or requiring specific treatment in asymptomatic patients).
LE	II-3
Number of patients & Patient characteristics	A total of 70 patients at risk of colorectal cancer were enrolled in the study. mean age 58.3 years (range 29 to 87) **Inclusion criteria** (1) patients at risk for CRC unable to undergo the colonoscopic examination because of the anaesthetic risk and co-morbidities (2) patients at risk for CRC who refused colonoscopy. Patients at risk for CRC: patients with personal or family history of adenomas or colorectal cancer, with digestive symptoms such as bleeding, recent bowel habits change, weight loss, anemia, abdominal pain, positive fecal occult blood test and suspect imaging abdominal ultrasound, computed tomography (CT)/positron emission CT scan were included in the study. **Exclusion criteria** (1)patients with pacemakers; (2)patients with suspected digestive stenosis or intestinal occlusion; (3)patients with dysphagia or swallowing disorders.
Intervention	PillCam Colon 2 (CCE2) Given Imaging Ltd
Comparison	
Length of follow up	
Outcome measures / Effect size	• CCE2 showed positive findings in 23 patients (34%, 95%CI: 21.6%-44.1%) • The significant lesions reported were: polyps > 6 mm in five patients, ≥ 3 polyps in 10 patients, multiple colonic angiomas in 2 patients, colon cancer in 4 patients, other digestive cancers in 2 patients, a newly discovered Crohn's disease in 1 patient and radiation enteritis in another. • A total of 19 patients had insignificant lesions (17 with diverticulosis,1 with ulcerative colitis and inflammatory pseudopolyps and 1 with a < 6 mm polyp). The **capsule excretion rate** in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95% CI; 13.7%-34.1%). Every patient accepted CCE as an alternative exploration tool and 65/70 (93%) agreed to have another future control by CCE. **Adverse event** No complications were reported during or after CCE examination. **Conclusion:** PillCam Colon 2 capsule was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy.
General comments	Funding: ESGE-GIVEN research grant

Bibliographic citation	3. Triantafyllou K, Viazis N, Tsibouris P, Zacharakis G, Kalantzis C, Karamanolis DG, Ladas SD. Colon capsule endoscopy is feasible to perform after incomplete colonoscopy and guides further workup in clinical practice. Gastrointest Endosc. 2014;79:307–316.
Study type/Method	Prospective, follow-up study. Setting: Three tertiary-care centers. **Objective:** To investigate the extent that CCE complements incomplete colonoscopy and guides further workup Patients underwent CCE either immediately after colonoscopy or were rescheduled. Further investigations were guided by the results of CCE
LE	II-2
Number of patients & Patient characteristics	75 outpatients Patients: Consecutive outpatients after colonoscopy failure
Intervention	PillCam Colon 1 CCE1 Given Imaging Ltd
Comparison	No comparator
Length of follow up	2 years
Outcome measures / Effect size	• One third of the patients underwent CCE immediately after colonoscopy. • Overall, in 68 patients (91%), CCE reached or went beyond the colon segment at which colonoscopy stopped. • CCE technically complemented difficult colonoscopy of whether same-day CCE was performed (24 [96%]) or was not performed (44 [88%]). • CCE detected additional significant findings in 36% of the same-day CCE cases and in 48% of the rescheduled ones. • Two patients in the same-day group and 13 in the rescheduled CCE group underwent further colon examination that revealed additional significant findings in 3 of them. • 63 participants (84%) were willing to repeat CCE,if needed. • Follow-up has not identified symptomatic missed colon cancers. **Safety profile** 10% of patients reported mild adverse events (AE). Limitations: Selected patient population, first-generation colon capsule, old preparation scheme. **Conclusion:** CCE performed immediately or at a scheduled date after colonoscopy failure is feasible and safe. CCE after incomplete colonoscopy appears to yield significant findings, guide further workup, and has high patient acceptance.
General comments	

Bibliographic citation	4.Adler SN, Hassan C, Metzger Y, Sompolinsky Y, Spada C. Second-generation colon capsule endoscopy is feasible in the out-of-clinic setting. Surg Endosc. 2014;28:570–575
Study type/Method	Feasibility study **Objective:** To evaluate the feasibility and efficiency of CCE when offered as an out-of-clinic procedure. Patients with known or suspected colonic diseases who had up to 40 min of travel time from clinic to home were offered CCE as an out-of-clinic procedure. These patients were provided with four numbered vials (1 with metoclopramide, 2 with sodium phosphate, 1 with bisacodyl) and detailed instructions on how to interact with data-recorder automatic signaling. Patient compliance with data-recorder instructions, CCE excretion, and detection rates were prospectively assessed.
LE	II-3
Number of patients & Patient characteristics	41 patients (29 men) with a mean age of 57 years
Intervention	PillCam Colon 2 CCE2 Given Imaging Ltd
Comparison	colonoscopy
Length of follow up	
Outcome measures / Effect size	• At CCE-2 reading, lesions size 6 mm or larger were detected in 10 (24 %) of the 41 patients. • Nine of these patients (90 %) underwent a workup colonoscopy within a few months after the colon capsule procedure. • The findings of CCE-2 were confirmed in all cases. One patient with a lesion larger than 18 mm reported by CCE-2 eventually had a 25-mm sigmoid adenocarcinoma diagnosed. • One patient (10 %) was lost during the follow-up period. **Capsule excretion** In 85 % of the cases, the CCE2 was excreted within the battery operating time. **Conclusions** • As an out-of-clinic procedure, CCE2 is feasible and easily performed. • A home-based procedure may be associated with better acceptability and potentially with increased adherence to Colorectal cancer screening.
General comments	

APPENDIX 7

LIST OF EXCLUDED STUDIES

1. Spada C, Hassan C, Costamagna G. Virtual chromoendoscopy: Will it play a role in capsule endoscopy? Digestive and Liver Disease. 2011; 43(12):927-928.

2. Singhal S, Walia R, Balasubramanian G et al. Colorectal Cancer Screening Above Age 75: Outcomes of Colonoscopies in Symptomatic African American and Hispanic Adults. Gastrointestinal Endoscopy. 2009; 69(5):AB106.

3. Silva de Mojica C. Toward embedded detection of polyps in WCE images for early diagnosis of colorectal cancer.

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14. Weissfeld JL, Schoen RE, Pinsky PF et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. J Natl Cancer Inst. 2005; 97(13):989-997.

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17. Taylor SA, Greenhalgh R, Ilangovan R et al. CT colonography and computer-aided detection: effect of false-positive results on reader specificity and reading efficiency in a low-prevalence screening population. Radiology. 2008; 247(1):133-140.

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