Healthcare Improvement Scotland | SHTG Advice on health technologies

SHTG Recommendation 01
August 2020

In response to a request from the Scottish Government

Second-generation colon capsule endoscopy (CCE-2) for the detection of colorectal polyps

Recommendation for NHSScotland

CCE-2 should not replace optical colonoscopy, but should be available as a diagnostic option in the current pathway for patients who present with lower gastrointestinal signs and symptoms suggestive of colorectal cancer and have a positive faecal immunochemical test (FIT). Evidence on clinical effectiveness and economic analysis indicate that CCE-2 should be reserved for patients at lower risk of colorectal cancer.

Communication with patients needs to be very clear in setting out why they are being offered CCE-2. Shared patient decision-making should take into account the relative risks of incorrect diagnoses in each available investigative procedure, and should acknowledge that a substantial proportion – approximately half - of CCE-2 recipients will require a follow up procedure.

Support should be provided to patients undergoing bowel cleansing to ensure the efficacy of CCE-2, recognising the increased requirements surrounding the CCE-2 bowel preparation regimen compared with colonoscopy and computed tomographic colonography.

The full cost effectiveness of CCE-2 remains unknown. Based on the SHTG cost analyses, CCE-2 appears to increase financial cost for the health and care system.

SHTG supports the introduction of a registry to continuously and consistently collect relevant patient outcome and cost data, and this should inform future service delivery.

The COVID-19 pandemic has had a considerable impact on access to existing optical colonoscopy services. The provision of a CCE-2 service may offer additional capacity to help meet colonoscopy demand.

NHSScotland is required to consider the Scottish Health Technologies Group (SHTG) recommendation.

What were we asked to look at?

The Scottish Health Technologies Group (SHTG) was asked to assess the clinical and cost effectiveness of PillCam™ Colon-2 (second-generation colon capsule endoscopy (CCE-2)), compared with optical colonoscopy or computed tomographic colonography (CTC), for identifying colorectal polyps in adults with signs or symptoms of colorectal cancer or at increased risk of colorectal cancer.

Why is this important?

In 2018, Evidence Note 86 examined the evidence for CCE-2. Since then further evidence assessing the effectiveness of CCE-2 has been published.

A project between the Scottish Government and CCE-2 industry colleagues, called the Scottish Capsule Programme (SCOTCAP), aimed to ease pressure on waiting times for optical colonoscopy. SCOTCAP was delivered in the North of Scotland and was a feasibility and acceptability trial of the use of CCE-2 in the community. In order to inform decision making surrounding the rollout of SCOTCAP across Scotland, the Scottish Government asked SHTG to reassess the CCE-2 evidence.

What was our approach?

We produced an SHTG Recommendation based on a review of the published evidence assessing diagnostic accuracy and safety, recent results from the SCOTCAP trial, an SHTG costing analysis, and input from a patient representative group.

What next?

The Scottish Government and NHS Boards will consider the findings of this review when making decisions about future use of CCE-2 in clinical practice – particularly in-light of the COVID-19 pandemic and the subsequent resumption of routine NHS services.

Key points

- The body of literature for clinical use of CCE-2 for detection of colorectal polyps in people with signs or symptoms or at increased risk of colorectal cancer was broad. There was variation in population assessed, the comparator intervention, the setting of delivery and the measure of diagnostic accuracy used (see table 10).
- The most robust evidence on the accuracy of CCE-2, in people scheduled to undergo optical colonoscopy for known or suspected colorectal disease, remains the meta-analysis of five prospective studies (n=361) described in Evidence Note 86. The per-patient sensitivity for the identification of polyps ≥ 6 mm was 87% and per-patient specificity was 76%, using optical colonoscopy as the reference standard. All studies included in the meta-analysis were at risk of inclusion and exclusion bias.
- When this diagnostic accuracy was applied to data from the Scottish bowel screening programme this generated a negative predictive value of 90% and a positive predictive value of 70% for polyps ≥ 6 mm. If CCE-2 were used in a patient group at higher risk of colorectal cancer the negative predictive value would decrease.
- Three prospective cohort studies compared CCE-2 to CT colonography (CTC). One study (n=97) reported a statistically significant two-fold increase in relative sensitivity of CCE-2 compared with CTC for a polyp cut off point of ≥ 6 mm in people with an incomplete optical colonoscopy. The second study (n=48) found no difference in diagnostic yields in a similar patient group (people who had declined an optical colonoscopy). The third study (n=54) found no difference in diagnostic accuracy between CCE-2 and CTC in people who had a positive faecal occult blood test (FOBT) at 6 and 10 mm cut-off points.
- Three feasibility studies (n=729) indicated that CCE-2 can be delivered as part of a community based pathway. One of the studies (SCOTCAP, n=435) recruited patients in Scotland with lower gastrointestinal symptoms suggestive of colorectal cancer and surveillance patients. Patients swallowed the CCE-2 in a regional hub and were then discharged home before being followed up the next day.
- Six out of the seven polyp matching algorithms used in included studies allowed for a 50% measurement error in size. If use of CCE-2 in clinical practice is to reflect the diagnostic accuracy in the literature, then a cut-off of 3 mm must be set on CCE-2 to ensure detection of polyps ≥ 6 mm diameter.
- Five studies explored patient experience and preference of CCE-2 over optical colonoscopy and CTC. Results of preference varied, as did the populations consulted, but the two studies which examined discomfort reported less discomfort for CCE-2 compared with optical colonoscopy.

- A submission from a patient representative organisation, Bowel Cancer UK, highlighted that attention is needed when communicating with patients to ensure that: patients fully understand the care pathway and any potential delays in receiving results; that the bowel preparation for CCE-2 is more intense and uncomfortable than optical colonoscopy; and that additional procedures may be required.
- A *de novo* costing analysis based on data from the SCOTCAP project showed that the introduction of CCE-2 into the colon cancer diagnostic pathway in NHSScotland is likely to generate an increased budget impact compared to current practice. Scenario analyses demonstrated that CCE-2 may be cost saving in the symptomatic patient group, on the basis that a negative CCE-2 finding results in the avoidance of more costly hospital-based follow-up procedures. The equivalent analysis for surveillance patients was not cost saving.
- Results from the *de novo* costing analysis are only relevant to patients who are referred to optical colonoscopy upon presenting to primary care with lower gastrointestinal symptoms (symptomatic) or due to personal or family history of colon cancer (surveillance). Patients who take part in the Scottish Bowel Screening programme were excluded from the CCE-2 target population.
- Two systematic reviews in Evidence Note 86 reported a CCE-2 retention rate of 0.8% and an aspiration rate of 0.1%. No new secondary evidence on safety outcomes was identified.

Scottish Health Technology Council Considerations

The following points capture the Council's deliberations towards agreeing the final recommendation (Council meeting date 29th July 2020).

- The Council heard that, since Evidence Note 86, additional evidence included further published primary studies, outcomes reported from the SCOTCAP trial showing the feasibility of implementing a CCE-2 pathway in Scotland, a budget impact analysis of the SCOTCAP study, and a patient organisation submission from Bowel Cancer UK. No cost effectiveness studies were identified.
- The Council noted the innovative nature of CCE-2 and the prospect of further development of this and similar technologies. The Council highlighted the potential innovation this brings, particularly for those living in remote areas of Scotland, but noted that the potential benefits need to be balanced with an understanding of the effectiveness and risks, so that doctors and patients can make informed choices.
- The Council discussed the potential for missed diagnoses amongst all investigative modalities. Based on the evidence available to the Council, the risk of missed diagnosis appears higher with CCE-2 compared with colonoscopy.

- The Council had concerns around the relative accuracy of CCE-2 and noted that the risk/benefit ratio worsened with increased risk of colorectal cancer. The Council agreed that the identification of patients who were at the lower end of the risk spectrum would maximise the benefits of CCE-2 while limiting missed diagnoses and the requirement for additional procedures.
- The Council discussed the rigour of CCE-2 bowel preparation compared with colonoscopy. For frail patients, who may already have a lower tolerance to colonoscopy, it was reiterated that CCE-2 would not be suitable for this patient group.
- The Council heard that CCE-2 will likely be cost inducing, driven by the majority of participants in the SCOTCAP trial requiring further investigative procedures. Modelling was based upon a proportion of patients with negative CCE-2 findings not requiring follow up; resource savings from the reduction in colonoscopy procedures were then offset against the additional cost of CCE-2. While CCE-2 is cost inducing, Council noted it was a cheaper and potentially more sustainable option than outsourcing or extending NHS provided colonoscopy services to achieve increased capacity.
- The Council highlighted the importance of longer-term monitoring of costs and outcomes. The further development of the existing SCOTCAP study registry, to a national registry, is vital to ensure continuous evaluation and inform future service delivery and technology development.
- The Council heard of the benefit of supportive pictorial information for patients about the pathway and the risk and benefits of investigation. The Council were supportive of the development of this information.
- The Council acknowledged that its role is to provide an independent view on the use of health technologies in Scotland. The Council recognised the current status of colonoscopy waiting lists and strain on services during the COVID-19 pandemic. The Council noted the Scottish Government's decision to progress to a rapid adoption of CCE-2 to support endoscopy recovery, and associated guidance. Further guidance, taking into account patient outcome data and colonoscopy service capacity, should be developed in due course.

Contents

Definitions

Adenoma: a type of bowel/colorectal polyp that may develop into cancer if not removed[1].

Anal verge: the end of the anal canal where the anal wall meets the external skin[2].

Bowel/colorectal polyps: small abnormal tissue growths in the inner lining of the colon or rectum[3].

Haemorrhoidal plexus: a network of veins that surround the lower part of the rectum[2].

Faecal occult blood test (FOBT)/faecal immunochemical test (FIT): tests used in the Scottish national bowel screening programme to detect small amounts of blood in stool samples[4].

A list of abbreviations are provided in appendix 1.

Definitions of terms relating to diagnostic test accuracy are provided in appendix 2.

Literature search

In 2018 Evidence Note 86[5] was published by the Scottish Health Technologies Group (SHTG). The 2020 SHTG assessment builds upon Evidence Note 86 based on the same research question; the same search strategy was used and search results were limited to studies published since the 2018 search.

A systematic search of the secondary literature was carried out between 27 and 28 January 2020 to identify systematic reviews, health technology assessments and other evidence based reports. Medline, Medline in process, Embase, Cinahl and Web of Science databases were searched for systematic reviews and meta-analyses. Simultaneously, and using the same databases, a search of the primary literature was conducted to identify studies that explored the diagnostic accuracy of CCE-2 in specific groups of patients not included in the secondary evidence.

A separate search was carried out on 25 February 2020 to identify literature on patient experiences and preferences relating to CCE-2 and other colon imaging tests. The Medline, Medline in process, and Cinahl databases were searched.

All search results were limited to English language and studies published since 2018.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies.

Concepts used in all searches included: capsule endoscopy, PillCam and capsule colonoscopy. A full list of resources searched and terms used are available on request.

Introduction

The colon is the first 1.5 m of the large intestine[6]. Colorectal (bowel) cancer begins in the inner lining of the colon or the rectum, often as a small growth called a polyp or adenoma. If left untreated polyps may eventually become cancerous, grow into the muscle layers of the large intestine and then spread through the colon wall to nearby organs such as the bladder. Early detection and removal of precancerous polyps is very effective for preventing colorectal cancer[7]. People in Scotland with signs or symptoms of colorectal polyps or cancer, or with a positive bowel screening test, are routinely referred for an optical colonoscopy.

Optical colonoscopy is an outpatient procedure that allows clinicians to examine the inside of the colon[8]. A flexible tube with a small light and camera at one end, called a colonoscope, is inserted through the anus and passed along the colon. Images from the colonoscope camera are displayed on a TV screen. If any polyps or abnormal tissues (lesions) are identified during the optical colonoscopy, a biopsy can be taken or the polyp removed as part of the procedure. During optical colonoscopy patients receive sedation, painkillers and air insufflation of the colon.

Optical colonoscopy is the current reference standard for examining the colon lining[9]. In approximately 5% to 20% of patients referred for optical colonoscopy, the procedure cannot be completed[10, 11]. This may be due to poor adherence to the bowel cleansing regimen, unusual anatomy obstructing the colonoscope, or patient intolerance of the procedure[9, 12]. Some patients are unable to have an optical colonoscopy due to elevated bleeding or sedation risks. Patients in Scotland with an incomplete optical colonoscopy or unable to undergo optical colonoscopy may have a computed tomographic colonography (CTC) instead. Frail elderly patients may be unable to undergo optical colonoscopy due to the bowel cleansing required and may therefore have a CTC[13]. CTC allows colon examination by producing a 3D reconstruction of the inside of the colon using CTC imaging[9]. The scan itself is quick -taking only a few seconds - yet patients need to consume barium-sulphate or iodine-based contrast materials, still require air insufflation, and are exposed to potentially harmful ionising radiation.

Colon capsule endoscopy (CCE) is a non-invasive technique for examining the colon using a small capsule containing one or more cameras. Colon capsule endoscopy does not involve sedation, patient exposure to ionising radiation or air insufflation of the colon[12]. However, unlike optical colonoscopy it is not possible to biopsy or remove suspicious polyps during the CCE procedure. Use cases for CCE include the detection of colorectal polyps and cancer in patients unwilling or unable to have an optical colonoscopy, patients with an incomplete optical colonoscopy, patients who would currently receive CTC, or as an initial 'triage' investigation in patients referred for optical colonoscopy.

Optical colonoscopy, CTC and CCE all require patients to undergo a period of bowel cleansing to ensure the lining of the colon is clearly visible on images. The composition and intensity of the bowel cleansing regimen varies between imaging modalities, with the most intensive bowel cleansing being used for CCE and the least intensive used for CTC. Due to the use of bowel cleansing in all colon

imaging procedures and the variation in bowel cleansing regimens for each imaging modality it was not possible to consider these processes in detail in this rapid review which focused on the effectiveness of the CCE device. It is likely that the real world diagnostic accuracy of all three tests, CCE, optical colonoscopy and CTC, will depend on the effectiveness and adherence to the bowel cleansing regimen.

The diagnostic accuracy of CCE is also likely to be affected by the expertise and accuracy of individuals interpreting the images following completion of the procedure. Evaluation of the requirements for accurate interpretation of CCE images is outwith the scope of this rapid review.

Health technology description

Colon capsule endoscopy involves three key components: an ingestible capsule endoscope; a data recording device worn by the patient throughout the procedure; and image processing software[9, 12]. A first-generation PillCam™ Colon was replaced with the second-generation PillCam™ Colon 2 (CCE-2) in 2009 (Medtronic plc, Dublin, Ireland). In CCE-2 the camera frame rate and angle of view have been increased and the data recorder procedure simplified[14]. This review only considers evidence on second-generation CCE. CCE-2 is the main colon capsule technology currently on the market in the UK. The size of CCE-2 capsule is 11.6mm by 31.5mm and it has an approximate battery life of ten hours. The capsule consists of two cameras, each with a 172 degree angle of view, light emitting diodes to illuminate the area around the cameras and bidirectional wireless communication technology. The cameras have an adaptive frame rate which allows CCE-2 to take more images when moving through the colon and fewer images when stationary or in other parts of the body.

The data recording device is approximately the size of a human hand and consists of a small screen with a socket for attaching sensor leads. The data recording device is worn in a pouch at hip level with a strap over the patient's shoulder. Sensor leads from the data recording device are attached to the skin under clothing.

Patients swallow the colon capsule endoscope following a period of bowel cleansing similar to, but more intensive than, that used for optical colonoscopy[9, 12]. Thorough cleansing of the bowel prior to swallowing the capsule is essential as small amounts of debris remaining in the colon can impede progress of the capsule or prevent clear visualisation of the colon lining[12]. A typical bowel cleansing regimen for CCE-2 involves ingesting four litres of polyethylene-glycol solution in a split dose of two litres at a time and taking one or more 'boosters', such as sodium phosphate, to increase the capsule excretion rate. This bowel cleansing regimen is performed by the patient at home over the 48 hours prior to CCE-2 examination.

Transit of CCE-2 through the digestive system takes up to ten hours depending on the individual. The capsule is swallowed under clinical supervision and the patient can return home after successfully ingesting the capsule[9]. Once the capsule has been excreted the images are downloaded from the recording device to a computer with image processing software such as the RAPID® software for CCE-2 which converts images into time-compressed video format for easier viewing[9, 12]. Reading and

interpretation of CCE-2 images requires skilled personnel and can be out-sourced to non-NHS organisations that specialise in CCE-2 image interpretation.

Colon capsule endoscopy is not routine practice across Scotland. The manufacturer of CCE-2 propose that CCE-2 could be used in four groups of patients:

- Patients with a positive faecal immunochemical test (FIT) from the bowel cancer screening programme – as a triage tool prior to optical colonoscopy,
- Patients under surveillance following previous positive findings on optical colonoscopy,
- Patients with an incomplete optical colonoscopy despite adequate bowel preparation, and
- Patients with contraindications for optical colonoscopy or sedation, but who could undergo optical colonoscopy should abnormalities be identified on CCE-2.

Epidemiology

Colorectal polyps affect approximately one in four people at some stage in their life[3]. Most colorectal polyps are not malignant, but if polyps are not removed they can eventually become cancerous. A polyp ≥ 6 mm or three polyps of any size are considered clinically significant and polyps ≥ 10mm are associated with advanced adenoma[7]. Most colorectal cancers develop from precancerous polyps[7, 15].

Colorectal cancer is more common in people aged over 50, with approximately 95% of colorectal cancer diagnoses in this age group[16]. Other groups at increased risk of colorectal cancer include people with signs or symptoms, such as rectal bleeding or an abdominal mass, and first-degree relatives of patients with colorectal cancer[7].

Colorectal cancer is the third most common cancer in Scotland with 3,776 new diagnoses in 2017 and 1,687 people dying from the disease in the same year[16]. Over the past decade, during which the national bowel screening programme was introduced, colorectal cancer incidence and mortality rates have been declining in Scotland.

Table 1 summarises Scottish data on patients referred for optical colonoscopy following a positive bowel cancer screening test[15]. Seventy-seven percent of patients referred for optical colonoscopy following a positive screening test between 1 November 2016 and 31 October 2018 attended for the procedure. The rate of incomplete optical colonoscopy (4.6%) and complications following optical colonoscopy (0.5%) were low. It should be noted that while uptake of testing is rising, only 59.5% of eligible adults completed the bowel screening test during this period.

Table 1: optical colonoscopy data for patients referred from the Scottish bowel screening programme between 1 November 2016 and 31st October 2018 inclusive[15]

	Positive screening test*, n	Colonoscopies performed, n (%)	Incomplete colonoscopies, n (%)	Complications following optical colonoscopy**, n (%)
Male	16,117	12,523 (77.7)	413 (3.3)	55 (0.44)
Female	12,462	9,558 (76.7)	602 (6.3)	44 (0.46)
All persons	28,579	22,081 (77.3)	1,015 (4.6)	99 (0.45)

**The bowel screening test in Scotland has changed from FOBT to FIT in November 2017*

***These figures should be regarded with caution as there is no standard reporting process for optical colonoscopy complications in Scotland*

In the Scottish bowel screening programme a positive test from a quantitative FIT is 80 µg Hb/g faeces and above[17]. As part of the response to the coronavirus pandemic the Scottish Government offered guidance on the use of FIT when a patient presented with lower gastrointestinal symptoms suggestive of colorectal cancer[18]. During the period when endoscopy services were most restricted, clinicians were advised to only refer patients with symptoms and a FIT result ≥ 400 µg Hb/g faeces for further investigation. As COVID-19 restrictions ease and endoscopy services restart, patients with symptoms and FIT result ≥ 400 µg Hb/g faeces were referred for urgent investigation and patients with symptoms and FIT result > 10 to < 400 µg Hb/g faeces were referred for routine investigation. The Scottish Government stated that these were guidelines and not a substitute for clinical judgement.

Clinical effectiveness

Both false positive and false negative results from colon examination have undesirable implications. People receiving a false positive result may be subjected to unnecessary medical procedures, usually optical colonoscopy, which carries risks to the patient and costs to the service. People receiving a false negative result may be at risk of progressing to colorectal cancer before being correctly diagnosed. Tests with high sensitivity for detecting clinically relevant colorectal polyps are desirable. Optical colonoscopy is the reference standard for colon examination and is therefore used to calculate diagnostic accuracy measures such as sensitivity and specificity[9]. Several of the populations of interest were, by definition, unable or unwilling to have an optical colonoscopy. Consequently primary studies often reported alternative measures of diagnostic performance, such as diagnostic yield or detection rate.

Evidence Note 86

The evidence on using CCE-2 to detect colorectal polyps/cancer consisted of one systematic review with meta-analysis[7] and seven primary studies that were not included in the meta-analysis, as they related to different patient populations, or were published after the review inclusion period[10, 11, 19-23].

The meta-analysis comprised two studies which included participants identified with a positive faecal occult blood test (FOBT), and three studies which included a mix of screening, lower GI symptoms and surveillance patients[7].

Of the seven primary studies, one was a prospective back-to-back study comparing the results of CCE-2 and optical colonoscopy following a positive FIT as part of the national screening programme[21]. Two were prospective cohort studies evaluating the use of CCE-2 for screening first-degree relatives of patients with colorectal cancer diagnoses[20, 22], both comparing CCE-2 with optical colonoscopy. Two were prospective cohort studies investigating the use of CCE-2 in patients with a previous incomplete optical colonoscopy: one compared CCE-2 with CTC[23], the other reported diagnostic yield for CCE-2[11]. One study was a prospective cohort that examined the use of CCE-2 in 70 patients at increased risk of colorectal cancer but unable or unwilling to undergo optical colonoscopy[10]. The final study was a single-arm prospective pilot study evaluating the feasibility of providing CCE-2 colonic examination in an out-of-clinic/home setting for patients with known or suspected colonic disease in Israel[19].

The full clinical effectiveness literature review from Evidence Note 86 can be found in appendix 3.

Clinical effectiveness update

Since the publication of Evidence Note 86 there have been six relevant studies published and one relevant unpublished study. Five were prospective cohort studies[24-27], one was a retrospective cohort study[28], and one a randomised controlled trial (RCT)[29]. The patient groups within the primary studies varied, as did the purpose of the studies, meaning that diagnostic accuracy was often a secondary outcome. Less informative measures of diagnostic accuracy were often used, for example diagnostic yield.

No new secondary evidence reporting diagnostic accuracy of CCE-2 was identified.

Two of the prospective cohort studies explored using CCE-2 in patients with incomplete optical colonoscopies due to reasons other than insufficient bowel preparation[24, 25]. The measure of diagnostic performance in both studies was incremental diagnostic yield. The retrospective cohort study evaluated using CCE-2 as a screening modality in patients who had a previous incomplete colonoscopy, and confirmed results with an optical colonoscopy[28]. The reason for referral to optical colonoscopy varied and the study reported per-polyp sensitivity.

One study tested CCE-2 as a screening tool to identify patients requiring a therapeutic optical colonoscopy amongst patients who were under surveillance due to an increased risk of colorectal cancer[26]. This study reported diagnostic yield.

One prospective cohort study examined the use of CCE-2 for detection of neoplasia in a population with a positive FOBT test from a bowel screening programme[27]. This study reported per-polyp sensitivity, but using the data available per-patient sensitivity was calculated by SHTG[27].

The RCT compared CCE-2 with CTC in people who had refused an optical colonoscopy, following a positive FOBT[29]. The authors reported the diagnostic yield of both modalities and compared the diagnostic rates.

Finally, the Scottish Capsule Programme (SCOTCAP) explored the feasibility of a new clinical pathway that used CCE-2 in patients who were either under surveillance or were referred from primary care with lower gastrointestinal symptoms suggestive of colorectal cancer (Prof Angus Watson, Director of Research, Development and Innovation, NHS Highland. Personal communication, 16 April 2020). Diagnostic yield was reported in this study.

Patients with incomplete colonoscopy due to reasons other than insufficient bowel preparation

Two studies explored using CCE-2 in patients with incomplete optical colonoscopies due to reasons other than insufficient bowel preparation[24, 25]. The measure of diagnostic performance in both these studies was incremental diagnostic yield (percentage of participants with new lesions identified).

The first of these studies was a multi-centre prospective cohort study[24]. A failed optical colonoscopy was defined as not reaching the cecum or ileo-cecal anastomosis due to looping, angulation of the bowel, adhesions, intolerance of sedation, or inflammation. Following an incomplete optical colonoscopy, CCE-2 was carried out either the next day or within 30 days, with patients choosing which group they were assigned to. The group receiving CCE-2 the following day were given a low volume bowel preparation of MoviPrep™, then boosters of MoviPrep™, sodium picosulfate and a bisacodyl suppository. The group that underwent CCE-2 within 30 days had a 3-day preparation of clear liquids and MoviPrep™, and then the same boosters as the first group.

Polyp sizes and locations were recorded for both the incomplete optical colonoscopy and CCE-2, but were only reported for the optical colonoscopy. Incremental diagnostic yield was a secondary outcome in this study and defined as significant findings on CCE-2 in the colon segment not seen by the incomplete optical colonoscopy - this did not require a complete CCE-2 examination, just the missing segment from the optical colonoscopy.

Eighty-one participants were enrolled in the study and 74 were included in the final per-protocol analysis. Mean age was 66 years and 41% were male. Of the 74 patients included in the analysis, bowel cleansing was adequate in 48 (65%) and there were 48 (65%) complete CCE-2 examinations. Original reasons for referral to optical colonoscopy were screening for colorectal cancer (22%), anaemia (15%), bleeding (15%), irregular stool (12%), abdominal pain (12%), symptoms of inflammation (7%), colitis (5%) and other reasons (12%). Intention-to-treat analysis (n=81) produced an incremental diagnostic yield per patient for CCE-2 of 22% compared with incomplete optical colonoscopy. Per-protocol analysis produced an incremental diagnostic yield per-patient for CCE-2 of 24% compared with incomplete optical colonoscopy (table 2). Adverse events reported in this study included capsule retention in the small bowel due to fistulating Crohn's disease which required surgery (n=1), and nausea and vomiting follow the sodium picosulfate booster (n=1).

Table 2: per patient incremental yield of CCE-2 segments missed by incomplete optical colonoscopy[24]

Analysis	Incremental diagnostic yield (per patient)
Intention-to-treat (n=81)	22%
Per-protocol (n=74)	24%

The second of the studies was a single centre prospective cohort study conducted in Ireland to explore the feasibility of using same-day CCE-2 in patients with incomplete optical colonoscopies[25]. Participants who had an incomplete optical colonoscopy for any reason other than poor bowel preparation received CCE-2 on the same day, a minimum of one hour recovery time after becoming alert post-procedure. Bowel preparation for optical colonoscopy included polyethylene glycol (MoviPrep™). Boosters for CCE-2 included intravenous metocloperamide, sodium phosphate, gastrografin and a bisacodyl suppository. Patients were allowed to return home after the capsule endoscope had reached the small intestine and the CCE-2 video was then examined the next day. Clinically significant polyps identified on the optical colonoscopy were removed at the time (n=6). Diagnostic yield was calculated, as well as the incremental diagnostic yield of complete CCE-2 examinations compared with incomplete optical colonoscopy.

Fifty participants were recruited over a 2-year period. Mean age was 57 years and 34% were male. Reasons for referral for optical colonoscopy included altered bowel habit (30%), iron deficiency anaemia (26%), peri-rectal bleeding (6%), abdominal pain (6%), polyp surveillance (6%), family history of colorectal cancer (8%), inflammatory bowel disease assessment (16%) and abnormal imaging (2%). Bowel cleansing was adequate in eight (16%) participants. In total 38/50 (76%) CCE-2 examinations were complete, defined as the CCE-2 device reaching the dentate line. The overall diagnostic yield for CCE-2 was 74%, with an incremental diagnostic yield of 38% for all polyps. Of the 19 participants who had polyps, seven (36%) were deemed clinically significant and referred for polypectomy: four patients had a polyp > 6mm and three patients had $\geq$ 3 polyps. Therefore incremental diagnostic yield of clinically significant polyps was 14% (Table 3). Adverse events included pain related to bowel preparation (n=2) and capsule retention in small bowel due to stricture from non-steroidal anti-inflammatory drug use which required resection (n=1).

Table 3: incremental diagnostic yield from CCE-2 in people who had an incomplete optical colonoscopy followed by same-day CCE-2[25]

	Optical colonoscopy (n=50)	CCE-2 (n=50)
	Diagnostic yield	Incremental diagnostic yield
All polyps	NR	n=19 (38%)
Clinically significant polyps ($\geq$ 6 mm or $\geq$ 3 polyps)	n=6 (12%)	n=7 (14%)

The two studies described here are potentially subject to bias due to the use of different definitions and a lack of confirmatory optical colonoscopy. In the first study, incremental diagnostic yield was calculated using only the incomplete sections of bowel from the optical colonoscopy[24]. In the second study the definition of incremental diagnostic yield also included the completed sections of bowel from the optical colonoscopy[25]. Neither study confirmed the results of the CCE-2 using a second optical colonoscopy. This lack of confirmation of CCE-2 results from incomplete bowel sections of the optical colonoscopy assumes the absence of false positives from CCE-2. Blinding was not mentioned in either study.

People with a previous history of incomplete optical colonoscopy and varied reason for initial referral

A retrospective single centre cohort study in Hiroshima investigated the diagnostic yield of CCE-2 in consecutive patients who had a previous incomplete optical colonoscopy[28]. Participants received CCE-2 usually within 3 months of their incomplete optical colonoscopy. If CCE-2 resulted in positive findings, participants were referred for an optical colonoscopy within a further 3 months for surgical resection of polyps. If there were no lesions identified on CCE-2, the participant was discharged from the study. The CCE-2 videos were examined by two independent endoscopists and disagreements settled by in-depth deliberation. Lesions were matched by colon segment or adjacent segment, and 50% of reference size. Lesions were recorded as 6-9 mm or $\geq$ 10 mm in size. Per-lesion sensitivity was calculated separately for superficial and protruded lesions. Confidence intervals were not reported. Only the per-protruded lesion sensitivity is reported in this review. If new protruded lesions were identified during optical colonoscopy these were regarded as false negatives for CCE-2. Bowel preparation was less intensive than other studies, comprising 1.5 L of polyethylene glycol electrolyte lavage solution after fasting on the day of the examination, and boosters consisting of dimethicone, metoclopramide, mosapride citrate, and magnesium citrate.

Sixty participants were enrolled in the study. Mean age was 61 years and 74% were male. Reasons for colonoscopy referral were positive FOBT (50%), follow up for ulcerative colitis (18%), previous small colorectal polyps (7%), history of melena (3%), anaemia (2%), diarrhoea (2%) and thickened appendix wall detected on computed tomography (2%). The number of patients is not reported here because the reported figures in the study did not add up to the total number of participants. It can be inferred from the reasons for referral that some patients were under surveillance and others were referred for initial investigation.

Following CCE-2 examination, 24 participants were discharged from the study as they received negative results (no lesions found). Thirty-four patients were referred for a follow-up optical colonoscopy and polyp resection. Two participants were excluded from the analysis due to inadequate bowel cleansing. The authors reported that two participants were excluded due to inadequate bowel cleansing but also stated that bowel cleansing was adequate in all patients. The authors reported a 94% completion rate for CCE-2, but calculated this as (32/34)*100. There was no explanation provided for the exclusion of the 26 participants with negative findings or incomplete

bowel preparation from this calculation. If all 60 participants who underwent a CCE-2 examination were considered, the completion rate would be 53%.

Forty protruded lesions were identified. Sensitivity for protruded lesions sized 6-9 mm was 83%, sensitivity for protruded lesions ≥ 10 mm was 100% and sensitivity for all protruded lesions was 88% (table 4). There were 11 false negatives from CCE-2 that were detected in the 34 participants who received a follow-up optical colonoscopy; six of these were superficial lesions and five were polyps. These diagnostic accuracy results were potentially subject to exclusion bias because there were 24 patients who received negative results from their CCE-2 examination and were discharged from the study. These patients did not receive a follow-up optical colonoscopy to confirm these negative findings. Therefore, the true false negative rate in this sample is unknown and sensitivity is likely to be overestimated. Adverse events were not mentioned as an outcome by the study authors.

Table 4: polyps detected, per-polyp sensitivity and false negatives in participants who had positive results from CCE-2 examination[28]

	6-9 mm	≥ 10 mm	All polyps
Protruded lesions detected (total n=40)	25/30	10/10	35/40
Per protruded lesions sensitivity	83%	100%	88%
False negatives protruded lesions*	-	-	n=5

*Found on optical colonoscopy but not CCE-2. Only protruded lesions are reported in this table.

Colonic surveillance in patients with previous neoplastic findings or a familial history of colorectal cancer

A prospective cohort study - using the population sample from an RCT investigating different types of bowel preparation for CCE-2[30] - evaluated the use of CCE-2 as a screening test to select patients from an optical colonoscopy surveillance population to receive a therapeutic optical colonoscopy[26]. Participants who took part in the RCT of CCE-2 bowel cleansing regimens were referred for an un-blinded optical colonoscopy if there were positive findings or the CCE-2 examination was incomplete. If there were negative findings on the CCE-2 the participants were discharged from the trial without further testing to check results. Size and colon segment location of polyps were recorded. Polyps were considered clinically significant if there were ≥ 3 polyps, were ≥ 10 mm in size, or any size of polyp if the participant had hereditary non-polyposis colorectal cancer. The endoscopists carrying out the optical colonoscopies were not blinded to the results of the CCE-2. Polyps on CCE-2 and optical colonoscopy were considered matched if they were 50% of reference size and in the same or an adjacent section of the colon. Any-size per-polyp sensitivities were calculated for both CCE-2 and optical colonoscopy using the sum of matched polyps and unmatched polyps from both modalities. This assumed that all polyps seen on CCE-2 but not optical colonoscopy were false negatives for optical colonoscopy, and all polyps seen on optical colonoscopy but not CCE-2 were false negatives for CCE-2.

In the RCT there were 180 participants. Mean age was 59 years and 52% were male. All patients were scheduled for a follow-up optical colonoscopy. Reasons for surveillance were a family history of colorectal cancer (41.1%), previous neoplastic findings in colorectal cancer screening (34.4%) and previous neoplastic findings in optical colonoscopy due to symptoms (24.4%). Bowel preparation regimens varied between participants, depending on RCT group allocation, but were combinations of magnesia tablets, MoviPrep™, domperidone and bisacodyl suppositories. Two of the groups also either took Eziclen™ or Gastrografin™.

From the 180 participants, CCE-2 examinations produced negative findings in 77 people who were then discharged from the trial. Bowel cleansing was adequate in 166 participants (92.2%) and the CCE-2 was excreted within the battery life in 127 cases (70.6%). There were 120 (67%) complete CCE-2 examinations. Due to positive findings (n=43) or an incomplete CCE-2 examination (n=60), 67 participants went on to have an optical colonoscopy and 36 a sigmoidoscopy. There were 29 participants who had both a complete CCE-2 and a full colonoscopy. From these 29 matched datasets the CCE-2 examination identified 120 polyps, while optical colonoscopy identified 76. The per-polyp sensitivity of CCE-2 was 88% (95% CI 82.8 to 93.6) and the per-polyp sensitivity of optical colonoscopy was 56% (95% CI 47.6 to 64.2) (table 5). All adverse events reported in this study were related to the bowel preparation regimens of the original RCT: severe vomiting (n=6), hunger discomfort (n=1), rash (n=1) and vaginal bleeding (n=1).

Table 5: per-polyp sensitivity of CCE-2 and optical colonoscopy for polyps of any size in participants with previous neoplastic findings or a familial history of colorectal cancer[26]

	CCE-2	Optical colonoscopy
Polyps detected (total n=136)	120	76
Non-matched polyps*	60	16
Per polyp sensitivity*	88% (95% CI 82.8 to 93.6)	56% (95% CI 47.6 to 64.2)

*From 29 patients with complete CCE-2 and complete optical colonoscopy

This study was potentially subject to bias as it assumed that all negative CCE-2 results (n=77) were true negatives. In addition, using the sum of all matched and unmatched polyps of CCE-2 and optical colonoscopy as a reference standard is unorthodox because optical colonoscopy is regarded as the gold standard. This approached removed the possibility of a false positive from both CCE-2 and optical colonoscopy. As the purpose of this study was to demonstrate the use of CCE-2 in a real-life clinical pathway as a screening tool and provide assistive data for optical colonoscopy this meant blinding was not appropriate. Even though the sample was large to begin with (n=180), the dataset used for calculating diagnostic accuracy was only 29 people.

CCE-2 in people with a positive test from a bowel screening programme

One prospective cohort study explored the use of CCE-2 in people with a positive test from a bowel screening programme in three centres in Italy and one in Spain[27]. The primary purpose of the study was to assess the diagnostic accuracy of CCE-2 for detecting advanced neoplasia, compared with optical colonoscopy. Within this they explored the diagnostic accuracy of CCE-2 for identification of colorectal polyps. The sample consisted of people with a positive FIT as part of a bowel cancer screening programme, who did not have a history of cancer or familial adenomatous polyposis. Participants received a CCE-2 examination and an optical colonoscopy the same day, and no more than 9 hours later. This allowed the same bowel cleansing regimen to be used for both procedures. The bowel cleansing regimen included senna tablets, polyethylene glycol, sodium phosphate, Gastrografin™ and a bisacodyl suppository. The CCE-2 video was examined by an endoscopist who was blinded to results of the optical colonoscopy.

Results from the CCE-2 examination were compared with the reference standard of the combined findings of two optical colonoscopies and true positives were defined as polyps seen on both the CCE-2 and optical colonoscopy examinations. Polyps seen on CCE-2 but not optical colonoscopy were regarded as false positives for CCE-2 and polyps not seen on CCE-2 but seen on optical colonoscopy were regarded as false negatives for CCE-2. Polyps were deemed clinically significant if they were $\geq$ 6 mm in size. Polyps were matched between the CCE-2 examination and the optical colonoscopy if two of the following criteria were satisfied: size within 50% of reference, location in segment of colon, and morphology (polypoid versus non-polypoid). Per-polyp sensitivity was calculated for a 6 mm cut-off point for optical colonoscopy referral. Confidence intervals were not reported. Per-patient sensitivity and specificity were not reported in the article but were calculated by SHTG using data which allowed calculation of per-patient diagnostic accuracy.

In total 222 participants were enrolled. Mean age was 61 years and 56% were male. Nineteen participants refused to swallow the capsule, and 25 CCE-2 examinations were incomplete due to slow transit. The remaining 178 (80%) participants had a complete CCE-2 examination and an optical colonoscopy. One hundred and fifty-seven (88%) had adequate bowel cleansing. Eighty-five participants received a clear negative result from CCE-2 in regard to polyps, and 93 were identified with clinically significant polyps. There were four cases of negative CCE-2 results but clinically significant polyps were then detected on optical colonoscopy (false negatives) and three negative results on optical colonoscopy which were positive on CCE-2 (false positive). Using these data, per-patient sensitivity for polyps $\geq$ 6 mm was calculated by the SHTG as 97% and per-patient specificity as 96% (table 6). There were no adverse events reported in relation to the CCE-2 examination but 25% of participants reported some sort of discomfort from the bowel cleansing regime: nausea, headaches, or abdominal pain.

Table 6: per-patient sensitivity and specificity in participants with positive FIT test and no history of cancer or familial adenomatous polypsis[27]

	CCE-2	Optical colonoscopy
Complete examination (both CCE-2 and colonoscopy)	178	
Negative result from CCE-2	85	-
Participants with polyps ≥ 6 mm detected	93	90
Participants with polyps ≥ 6 mm detected on optical colonoscopy but not CCE-2 (false negative)	-	4
Participants with polyps ≥ 6 mm detected on CCE-2 but not optical colonoscopy (false positive)	3	-
Per-patient sensitivity*	97%	-
Per-patient specificity+	96%	-

*sensitivity calculation: true positives/(true positives + false negatives) (90/(90+4))
+specificity calculation: true negatives/(true negatives + false positives) (81/(81+3))

The cohort study authors conducted per-polyp analysis based on the 90 participants who had true positives. CCE-2 detected 154 polyps ≥ 6mm in this sample. Optical colonoscopy detected 281 polyps of all sizes and 121 polyps ≥ 6mm. The study authors matched 139 polyps from the CCE-2 examination to polyps identified by optical colonoscopy. This implies that at least 18 of these matched polyps were not clinically significant as just 121 were identified by optical colonoscopy. Per-polyp sensitivity was calculated based on the 139 matched polyps. Per-polyp sensitivity for all polyps ≥ 6mm was reported as 84.8% when false negatives were included (n=10) and 90.3% when false negatives were excluded. No justification was provided for excluding 10 false negatives from the sensitivity calculation (table 7).

Unlike other studies, this study used a 'two out of three' criteria as their polyp matching algorithm. This may be the reason the CCE-2 had more matched polyps (n=139) than the optical colonoscopy identified as clinically significant (n=121). As stated earlier this implies that some polyps that were identified as not being clinically significant by the reference standard but were still matched. The results would be more robust if these were deemed false positives as the cut-off was set at 6 mm.

Table 7: per-polyp sensitivity in patients with a positive FIT test and no history of cancer or familial adenomatous polyposis[27]

	CCE-2	Optical colonoscopy
Number of polyps of all sizes (90 participants)	-	281
Number of clinically significant polyps ≥ 6 mm (90 participants)	154	121
Unmatched polyps from CCE-2 to optical colonoscopy	15	
Polyps matched for site, shape and size	107	
Polyps matched for site and shape only	11	
Polyps matched for site and size only	21	
Total polyps matched	139	
Per-polyp sensitivity (154 polyps, ignores false negatives from CCE-2)	90.3%	
Per-polyp sensitivity (164 polyps, 10 participants had clinically significant polyps at optical colonoscopy but not CCE-2)	84.8%	

Comparison of CCE-2 and CTC in patients with a positive FOBT and have refused an optical colonoscopy

An RCT carried out in 11 centres in France investigated the impact of inviting people who had a positive FOBT, but refused an optical colonoscopy, for either a CCE-2 or CTC[29]. As a secondary outcome this study compared diagnostic yield between CCE-2 and CTC. Participants were identified from two not-for-profit screening registers, and invited by letter to receive either CCE-2 or CTC. The letter to each person only offered one test modality. Diagnostic yield for each modality was reported for all positive findings, adenomas/cancers, clinically significant (≥ 6 mm) polyps and diverticulas. Bowel preparation included polyethylene-glycol solution, domperidone, sodium phosphate and a bisacodyl suppository.

In total, 756 potential participants were sent a letter offering either CCE-2 or CTC. Mean age of potential participants was 63 years and 49% were male. After non-responders and those unwilling to participate were removed, there were 20 participants in the CCE-2 group and 28 in the CTC group. Demographics were not reported for those who received CCE-2 or CTC. Eight participants had a complete CCE-2 (40%) and 26 had a complete CTC (93%). Bowel preparation was adequate in 15 (75%) of participants who received CCE-2 and 26 (93%) of participants who received CTC. More participants in the CCE-2 had positive findings compared with the CTC group (p=0.04), but there was no difference between the groups in detection of clinically significant polyps (p=0.49) (table 8). The poor uptake could indicate that participants who do not want an optical colonoscopy may also

refuse CCE-2, as only 19 out of 378 invited took the opportunity when offered. Adverse events were not reported as outcomes in this study.

Table 8: intention-to-treat analysis on diagnostic yield of CCE-2 and CTC in people with a positive FOBT who refused an optical colonoscopy[29]

	CCE-2 (n=19 + 1 CTC)	CTC (n=28)	p value
Positive findings	16 (80.0%)	13 (46.4%)	0.04
Polyps ≥ 6 mm	6 (30.0%)	5 (17.9%)	0.49
Adenomas/cancers	6 (30.0%)	3 (10.7%)	0.07
Diverticulas	4 (20.0%)	5 (17.9%)	>0.99

This study was subject to volunteer bias due to the low number of participants responding to the invitation letter. The randomisation process was not described nor if there was concealment. Participants and their GP were blinded to the existence of the group which raises ethical considerations of participants not being fully informed of the study they have consented to. The CCE-2 data may have been contaminated by one of the participants receiving CTC off-protocol and the data not being removed/transferred to the other group. Additionally the sample size was small and likely underpowered, and the number of detections even smaller. Lastly there was ambiguity in the statistical test used. The authors reported that, "*Categorical variables are presented as frequency (percentage). Quantitative variables were compared using the Wilcoxon test and qualitative ones were compared using the Pearson chi-squared test.*" However, there were no qualitative data collected and there was no indication of which test was used to calculate the p values.

SCOTCAP project

The SCOTCAP project was run between industry (Medtronic plc and Corporate Health International) and the Scottish Government (Prof Angus Watson, Director of Research, Development and Innovation, NHS Highland. Personal communication, 16 April 2020). The objective of the SCOTCAP project was to demonstrate the feasibility of a new clinical pathway that used CCE-2 in the community in patients who were either under surveillance or symptomatic for bowel cancer. This pathway was proposed to reduce waiting times for optical colonoscopies in this patient group.

The prospective SCOTCAP feasibility study was carried out in NHS Highlands, NHS Western Isles and NHS Grampian in Scotland. Patients were eligible for inclusion if they had lower gastrointestinal symptoms indicative of colorectal cancer and referred from primary care (positive FIT and no iron deficiency), or if they were on the surveillance waiting list for an optical colonoscopy following positive findings from a previous optical colonoscopy. After intensive bowel preparation, the patient travelled to one of seven regional hubs where they were given the CCE-2 device to swallow, after which they went home and returned the recorder the next day. If CCE-2 results were positive the patient was referred for further investigation. Polyps were considered clinically significant if they

were ≥ 6 mm. Diagnostic yield for CCE-2 in the SCOTCAP project was calculated using data provided to the SHTG. Data regarding the outcomes of follow up optical colonoscopies or flexible sigmoidoscopies are in the process of being collected, but are not available for this assessment.

Over a 6-month period in 2019, 435 patients were enrolled in the SCOTCAP study; 278 were symptomatic and 157 were under surveillance. Demographic data were not supplied. Following CCE-2, 61% of all patients were referred for either an optical colonoscopy or a sigmoidoscopy. It was not clear how many of these referrals were due to pathology and how many due to incomplete CCE-2 examination.

More detailed results for the NHS Highland subset of patients were provided. This subset made up the majority of participants (n=404) in the SCOTCAP study, with 128 under surveillance and 276 symptomatic. The completion rate for CCE-2 in the NHS Highland subset was 82%, with 101 complete exams in surveillance patients and 230 in symptomatic patients. The diagnostic yield was 50% overall, 54% for surveillance patients, and 49% for symptomatic patients (table 9). All patients with positive results were referred for either an optical colonoscopy or sigmoidoscopy for further investigation. Data were not supplied on the pathologies present and results from CCE-2 were not confirmed. Data on adverse events were not supplied.

Table 9: diagnostic yield of CCE-2 in surveillance and symptomatic patients from NHS Highland in the SCOTCAP trial

	Surveillance	Symptomatic	Total
Total n	128	276	404
Complete CCE-2 examination	101	230	331
Diagnostic yield	54% (n=55)	49% (n=112)	50% (n=167)

The results from the SCOTCAP study are limited by the lack of information regarding participant demographics, the lack of detail on positive findings, and no confirmation of results after patients received a follow-up investigation. These limitations may have been due to the study design, as this was a feasibility trial and assessing diagnostic accuracy was not an objective.

Summary of literature

Table 10 presents an overview of the CCE-2 diagnostic accuracy data from all the published evidence included in Evidence Note 86 and the current update review. The table demonstrates the between-study variability in the populations investigated and the outcomes used to measure diagnostic accuracy.

Table 10: diagnostic accuracy data overview for CCE-2, derived from all literature included in the current and previous SHTG review.

All results are percentages (95% confidence interval) rounded to no decimal places.

Study design	CCE-2/ OC/ CTC	Outcome measures							
		Per-polyp sensitivity	Per-polyp specificity	Per-patient sensitivity	Per-patient specificity	Negative predictive value	Positive predictive value	Diagnostic yield	Incremental diagnostic yield
People with known or suspected colorectal disease, inclusive of positive FOBT or FIT from a screening programme									
Meta-analysis (5 prospective studies)[7]	CCE-2 vs. OC (pooled results)	-	-	**≥ 6 mm**: 87 (77 to 93) **≥ 10 mm**: 89 (77 to 95) **Any size:** 89 (66 to 97)	**≥ 6 mm**: 76 (60 to 87) **≥ 10 mm**: 91 (86 to 95) **Any size:** 75 (45 to 91)	-	-	-	-
Out of clinic setting for patients with known or suspected colorectal disease									
Prospective back-to-back[21]	CCE-2 vs. OC	-	-	**≥ 10 mm**: 87 (83 to 91)	**≥ 10 mm**: 92 (89 to 95)	-	-	-	-
Prospective cohort[19]	CCE-2	-	-	-	-	-	-	**≥ 6 mm**: 24	-
Prospective feasibility (SCOTCAP)	-	-	-	-	-	-	-	**≥ 6 mm**: 50	-

Study design	CCE-2/ OC/ CTC	Outcome measures							
		Per-polyp sensitivity	Per-polyp specificity	Per-patient sensitivity	Per-patient specificity	Negative predictive value	Positive predictive value	Diagnostic yield	Incremental diagnostic yield
Asymptomatic first-degree relatives of colorectal cancer patients									
Prospective trial[22]	CCE-2 vs. OC	**≥ 6 mm**: 91 (81 to 96) **≥ 10 mm**: 89 (72to 96)	**≥ 6 mm**: 88 (82 to 93) **≥ 10 mm**: 95 (90 to 97)	-	-	**≥ 6 mm**: 96 (90 to 98) **≥ 10 mm:** 98 (94 to 99)	**≥ 6 mm**: 79 (67 to 87) **≥ 10 mm**: 75 (58 to 87)	-	-
Prospective pragmatic randomised open trial[20]	CCE-2 vs. OC	-	-	-	-	-	-	**≥ 10 mm**: 12	-
Patients who have had an incomplete optical colonoscopy									
Prospective cohort[23]	CCE-2 vs. CTC	-	-	-	-	-	**≥ 6 mm**: 96 (78 to 100) **≥ 10 mm**: 83 (37 to 99)	**≥ 6 mm**: 24 (17 to 34) **≥ 10 mm**: 5 (2 to 12)	-
Prospective cohort[11]	CCE-2 vs. OC	-	-	-	-	-	-	-	**≥ 6 mm**: 60*
Prospective cohort[25]	CCE-2 vs. OC	-	-	-	-	-	-	-	**≥ 6 mm**: 14
Prospective cohort[24]	CCE-2 vs. OC	-	-	-	-	-	-	-	**≥ 6 mm**: 24 (per-patient)

Study design	CCE-2/ OC/ CTC	Outcome measures							
		Per-polyp sensitivity	Per-polyp specificity	Per-patient sensitivity	Per-patient specificity	Negative predictive value	Positive predictive value	Diagnostic yield	Incremental diagnostic yield
Retrospective cohort[28]	CCE-2 vs. OC	**≥ 6 mm**: 83 **≥ 10 mm**: 100 **All polyps**: 88	-	-	-	-	-	-	-
Patients from a screening bowel cancer screening programme									
Prospective multi-centre[27]	CCE-2 vs. OC	**≥ 6 mm**: 84.8	-	**≥ 6 mm**: 97	**≥ 6 mm**: 96	-	-	-	-
Surveillance patients									
Prospective cohort[26]	CCE-2 vs. OC	**≥ 6 mm**: 88 (83 to 93)							
Patients unwilling/ unable to receive optical colonoscopy									
Prospective cohort[10]	CCE-2	-	-	-	-	-	-	**≥ 6 mm**: 34	-
RCT[29]	CCE-2 vs. CTC	-	-	-	-	-	-	**≥ 6 mm**: 80	-

Abbreviations: OC: optical colonoscopy

CI was not always reported in the literature. Only main results displayed here. Accuracy of second modality or sub-group analyses can be found in main text.

**Incremental diagnostic yield high due to inclusion of section missed by incomplete optical colonoscopy*

Safety

The adverse events reported in the primary studies identified by the updated literature search in 2020 were described at the same time as the clinical effectiveness for situational context. The following paragraphs replicate the safety-specific evidence reported in Evidence Note 86.

Safety concerns relating to the use of the CCE-2 device include capsule retention in the bowel, capsule aspiration, skin irritation from the sensor attachments, risk of proximity to electromagnetic fields and allergy to bowel cleansing materials[31]. There are contraindications to the use of CCE-2 in patients with known or suspected gastrointestinal obstruction, stricture or fistulas; patients with cardiac pacemakers or other implanted electronic devices; patients with swallowing disorders; and pregnant women[31, 32]. Safety issues relating to the CCE-2 bowel cleansing regimen include electrolyte imbalance in people with existing renal impairment and tolerability in the frail elderly[31].

Two systematic reviews were identified that reported on adverse event rates for colon capsule endoscopy[7, 33]. The systematic review with meta-analysis discussed in the clinical effectiveness section reported adverse events relating to CCE-2, CTC and optical colonoscopy[7]. Fourteen patients out of 357 (3.9%, 95% CI 2.4% to 6.5%) reported experiencing mild to moderate adverse events associated with CCE-2, mainly relating to bowel cleansing. Adverse events experienced by patients receiving CCE-2 (n=357) included difficulty swallowing the capsule (n=4), capsule retention (n=3) and technical failure of the capsule (n=5). Capsule retention, potentially the most serious CCE-related adverse event as it requires surgical or colonoscopic retrieval of the capsule, occurred in 0.8% (95% CI 0.2% to 2.4%) of study participants. Fourteen patients (3.9%) reported experiencing mild to moderate adverse effects associated with bowel cleansing prior to CCE-2 examination. These included headache, nausea, vomiting, abdominal pain and fatigue. Adverse events relating to optical colonoscopy included pain (n=2) and bleeding (n=1). The single study (n=50) reporting adverse events relating to CTC recorded ten cases of mild pain following bowel cleansing and two cases of severe pain during the procedure.

The second systematic review compiled cases of capsule aspiration[33]. Thirty-four cases of capsule aspiration were identified from the published literature; almost all cases related to small bowel capsule endoscopy and one related to the first generation PillCam™ Colon device. However the similarity in size of capsule endoscopy devices makes these cases relevant to CCE-2. Identified cases of capsule aspiration occurred mainly in older patients (78.9±7.8 years) many of whom had pre-existing comorbidities. In 77.2% of cases the patient showed immediate symptoms of capsule aspiration such as coughing. For eleven patients the aspiration was short-lived (seconds or minutes) and self-resolved; twenty other patients required intervention to retrieve the capsule, usually bronchoscopy. Capsule retrieval was uneventful for 93.3% of patients – one patient developed aspiration pneumonia and another died of unrelated causes. Based on the approximate number of capsule endoscopies in studies reporting capsule aspiration events the estimated capsule aspiration rate is 0.1%.

Patient and social aspects

Combining the search results from Evidence Note 86 and the updated literature search, there were five primary studies that explored patient experiences and preferences relating to CCE and other colon imaging technologies[22, 34-37].

Bowel Cancer UK, a patient organisation, provided a submission of patient experience based primarily on an evaluation of the SCOTCAP project.

Evidence Note 86

One study conducted in the UK explored tolerance and acceptability of optical colonoscopy, CTC and CCE-2 for colon examination[36]. Consecutive patients undergoing optical colonoscopy for symptoms (n=158), optical colonoscopy following referral from the national bowel screening programme (n=77), CTC (n=128) or CCE-2 (n=56) were asked to complete a survey about their experiences of the relevant procedure. Participants were asked to rate pain associated with the procedure using the Gloucester Comfort Score (GCS, scale 1–5: no, minimal, mild, moderate, severe); to quantify overall procedure tolerance using a visual analogue scale (VAS, high tolerance 0 – low tolerance 10); and to indicate their willingness to repeat the same test in future. Endoscopists performing optical colonoscopies also scored patient pain during the procedure.

Results from the patient tolerability and acceptability survey are summarised in table 11. Median age of patients was lower for CCE-2 than other groups and highest in the CTC group. Approximately 29% of patients undergoing CTC and 21% of patients receiving CCE-2 had previously had an incomplete optical colonoscopy. Eighteen percent of patients having CTC and 23% of patients receiving CCE-2 had previously refused an optical colonoscopy. Patients undergoing optical colonoscopy reported experiencing statistically significantly more pain than patients receiving CTC or CCE-2 ($p<0.001$). Overall patient tolerability of the procedure (VAS score) was statistically significantly better for CTC and CCE-2 compared with optical colonoscopy ($p<0.001$); CTC also scored statistically significantly better than CCE-2 ($p<0.001$). Endoscopists perceived fewer patients to have experienced moderate to severe discomfort following optical colonoscopy compared with patient self-scored pain: 24.2% versus 49.3%, $p<0.005$. There were also statistically significant differences in the proportion of patients in each group who experienced adverse effects relating to bowel cleansing ($p<0.0001$ for all comparisons).

Table 11: patient tolerance and acceptability of optical colonoscopy, CTC and CCE-236

	Optical colonoscopy	CT colonography	CCE-2
n patients	235	128	56
Median age, years (inter-quartile range)	Symptomatic 55 (18-88) Screening 68 (55 – 76)	71 (32 – 87)	41 (16 – 72)
% male	Symptomatic 44% Screening 38%	37%	29%
Mean GCS discomfort score (±standard error)	3.32±0.09 (mild/moderate pain)	1.96±0.08 (no/minimal pain)	1.30±0.09 (no/minimal pain)
Adverse events (bowel cleansing)	Nausea 16.4% Bloating 16.5% Pain 6.4%	Nausea 4.7% Bloating 0.8% Pain 2.4%	Nausea 39.3% Bloating 19.7% Pain 12.5%
Overall tolerability (VAS)	5.43	2.35	3.80
Willing to repeat test	93.6%	96.1%	85.7%

To explore the choice of colon imaging test in an informed, non-clinical population, members of the public recruited outside a local shopping centre (n=100) were provided with information about the tests and asked about their choice of procedure in the event they developed symptoms or were referred from the bowel screening programme. Participants received an extended patient leaflet outlining the advantages and disadvantages of each option, information about patient tolerance from the patient survey, advice that the tests had similar diagnostic sensitivity, and information about biopsy, immediate diagnosis with optical colonoscopy, non-completion rates, serious adverse events, identification of irrelevant pathology and radiation exposure. Forty-five percent of members of the public consulted stated that they would choose optical colonoscopy, 37% chose CTC and 18% selected CCE-2 for investigating bowel symptoms. A larger proportion of members of the public would elect to have an optical colonoscopy (71%) if they had been referred from the bowel screening programme.

Three other studies explored patient aspects relating to CCE-2 as a bowel screening test[22, 34, 35]:

- One study in first-degree relatives of patients with colorectal cancer (n=177), described in the clinical effectiveness section of Evidence Note 86 (Appendix 3), evaluated participant satisfaction with CCE-2 and optical colonoscopy as a secondary outcome[22]. On an unvalidated 10-point satisfaction rating scale, scores were high for both CCE-2 (9.1±1.9) and optical colonoscopy (9.4±1.0). When asked which test they would prefer for future bowel screening,

41% of participants opted for CCE-2, 23% for optical colonoscopy and 37% expressed no preference.

- Another study used maximum differences scaling (MDS) to assess the importance of 12 test characteristics to patients consecutively recruited from a primary care waiting room (n=92)[34]. Although participant opinions varied greatly, sensitivity of the test, risk of bowel perforation and the need for a second procedure following a positive result, were generally considered the most important test characteristics. The majority of participants (62%) chose optical colonoscopy as their preferred screening test, 10% opted for CTC and 23% selected CCE-2.
- The third study was a market research survey in screening-eligible, paid volunteers (n=308)[35]. There was risk of bias in this study from participant selection, payment for participation and manufacturer involvement in the survey design. More than half the participants who had previously refused an optical colonoscopy identified bowel cleansing and invasiveness of the procedure among the top three reasons for declining. The proportion of participants choosing screening with CCE-2 was greater in the group that had previously declined an optical colonoscopy, but decreased as the amount of information provided about screening tests increased.

Studies from 2018-2020

One study was identified in the updated literature search that related to patient experiences and preferences for colorectal imaging modalities[37].

The study was a mixed methods[37] quantitative and qualitative assessment of experience of CCE-2 and optical colonoscopy[21]. From the 253 participants who initially received a questionnaire about their experiences, 239 fully or partly answered the questionnaire on discomfort for CCE-2, and 238 fully or partly answered for optical colonoscopy. Ten of these participants then completed a semi-structured interview about their experiences[37]. Discomfort was measured using a numerical rating scale of 1-10 with categories of low (<4), moderate (4-6) and high (>6) levels of discomfort. For CCE-2, 88.5% (n=224) reported a low level of discomfort, 5.5% (n=14) moderate discomfort and 0.4% (n=1) a high level of discomfort. For optical colonoscopy, 35.2% (n=89) reported a low level of discomfort, 31.2% (n=79) moderate discomfort and 27.2% (n=70) a high level of discomfort. The study authors reported that there was a mean discomfort level difference three points that favoured CCE-2, and that this was statistically significant ($p<0.0001$). From the semi-structured interviews, advantages associated with CCE-2 were less pain, embarrassment and invasiveness. Disadvantages were size of CCE-2 capsules when swallowing, longer waiting time for results and, if there positive findings, the need for an additional optical colonoscopy. The home setting for CCE-2 made participants feel less restricted and less like 'ill patients', but there was apprehension about the technical challenges of having the equipment in their home.

Bowel Cancer UK patient organisation submission

Bowel Cancer UK submitted to SHTG the views and experiences of people who had received a CCE-2 examination. This patient organisation submission was based on a qualitative evaluation of the SCOTCAP project. The main points supplied by Bowel Cancer UK were:

- Communication with patients needs to be very clear in detailing why they are being offered a colon capsule examination, what to expect from the procedure, and that they may still need an optical colonoscopy at a later date.
- The timelines for getting results from CCE-2 need to be explained clearly to patients. Potential delays in getting results due to unavailability of qualified staff to assess the video, staff holidays, or absence, may cause anxiety.
- The bowel preparation required for a colon capsule examination can be a very unpleasant process for some people. This may cause additional difficulties if they have a long way to travel to the hospital/GP, or if they have to use public transport.

The full submission from Bowel Cancer UK can be found in appendix 4.

Cost effectiveness

Evidence Note 86

In Evidence Note 86 a primary economic analysis from Ontario, Canada was identified that assessed the cost-effectiveness of CCE-2 as an alternative to CT colonography in patients with known or suspected colonic disease and a positive finding from a previous test[38]. The analysis used a Markov model to estimate the incremental costs and life-years lost due to misdiagnoses of advanced colorectal polyps (>10mm). Branch probabilities within the decision-tree were based on a single study (n=54) within the systematic review with meta-analysis described in the clinical effectiveness section[7]. The results of this economic analysis may be misleading as the primary study used (Rondonotti et al, 2014) found no statistically significant differences in sensitivity or specificity between CCE-2 and CT colonography for detecting advanced adenomas (polyps >10mm)[7]. Details of the analysis are therefore not reported.

Studies published 2018-2020

One of the new primary studies identified in the updated literature search described the use of CCE-2 in a surveillance population as not being cost-effective, but did not provide any details of their analysis to support this statement[26].

De novo cost comparison analysis

SHTG was requested to conduct a cost comparison analysis that could be used as part of a Scottish Government business case for the SCOTCAP project. A full economic evaluation of the impact of CCE-2 has not been carried out. Equal diagnostic accuracy between CCE-2 and optical colonoscopy was assumed. Included costs were only those to the NHSScotland.

The cost analysis compares the current colon cancer diagnostic pathway with a new pathway that includes CCE-2, in two patient groups: surveillance and symptomatic. Screening patients with a positive FIT test have been excluded from the symptomatic population numbers as they are assumed to continue to undergo colonoscopy as part of the Scottish Bowel Screening Programme.

The existing optical colonoscopy pathway can be summarised as follows: patient referral; bowel preparation; travel to central optical colonoscopy facility; decontamination; and an operating theatre procedure carried out by a gastroenterologist. The CCE-2 pathway is delivered locally (from regional hubs), and provides an alternative to the optical colonoscopy theatre procedure.

The cost comparison analysis was carried out in two stages. The first is a per-pathway cost estimation where the average per patient costs were estimated for the optical colonoscopy pathway and the CCE diagnostic pathway. The second presents an aggregate annual cost impact with if CCE is introduced across all of Scotland. The models are built around the assumption that a proportion of CCE-2 patients, who would otherwise undergo optical colonoscopy, receive a negative CCE-2 diagnosis and therefore avoid colonoscopy which is a resource-intensive procedure. The models include a proportion of patients undergoing CCE who will subsequently be referred for additional examination with optical colonoscopy, flexible sigmoidoscopy or a CT scan. Reasons for subsequent referral include positive findings or incomplete CCE.

Target population

The target populations in the analysis are patients who were referred to optical colonoscopy upon presenting to primary care with lower gastrointestinal symptoms (symptomatic) or due to personal or family history of colon cancer (surveillance). Patients who had had an optical colonoscopy due to a positive screening test as part of the Scottish Bowel Screening programme have been excluded because they were not part of the SCOTCAP project. ISD data indicate that in 2018, there were 3,521 surveillance and 45,574 symptomatic patients in Scotland who would have been considered for CCE-2 had the service been available. These numbers are projected to grow annually at a rate of 0.34% based on average rates of planned optical colonoscopies in the 5-year period (2013-17).

Model parameters

Model parameters used in the analysis are presented in Table 12. Data on referral rates to subsequent tests following CCE-2 were obtained from SCOTCAP. All other parameters were informed by the literature and/or personal communication with clinical experts and NHS boards.

Please note: data within the following tables have been redacted where they are academic or commercial in confidence. All data were visible to the Council during their deliberations.

Table 12: Model parameters

Parameters		
CCE Eligibility rate		
CCE eligibility rate: surveillance patients	[redacted] %	SCOTCAP
CCE eligibility rate: symptomatic patients	[redacted] %	Expert opinion
Post-CCE referral rates		
Subsequent referral rate to optical colonoscopy (surveillance)	[redacted] %	SCOTCAP
Subsequent referral rate to flexible sigmoidoscopy (surveillance)	[redacted] %	SCOTCAP
Subsequent referral rate to optical colonoscopy (symptomatic)	[redacted] %	SCOTCAP
Subsequent referral rate to flexible sigmoidoscopy (symptomatic)	[redacted] %	SCOTCAP
Complications		
Major bleeding (optical colonoscopy)	0.37%	Scottish Bowel Screening Programme, KPI report, 2019
Colon perforation rate (optical colonoscopy)	0.08%	Scottish Bowel Screening Programme, KPI report, 2019
Major bleeding (flexible sigmoidoscopy)	0.03%	UK Flexible sigmoidoscopy screening trial 2002
Colon perforation rate (flexible sigmoidoscopy)	0.002%	UK Flexible sigmoidoscopy screening trial 2002
Follow-up tests (colonoscopy)		
Rate of incomplete optical colonoscopy	10%	Expert opinion
Rate of subsequent optical colonoscopy – current pathway- Surveillance	7.54%	Derived from ISD data for Scotland
Rate of subsequent optical colonoscopy – current pathway -Symptomatic	5.57%	Derived from ISD data for Scotland
Patient reimbursement		
% patients eligible for travel reimbursement (all Scotland)	2.97%	Various sources
% patients eligible for travel reimbursement (North)	7.20%	Various sources

Data have been redacted where they are academic or commercial in confidence. All data were visible to the Council during their deliberations.

Table 13 presents the cost data used in the analysis. The main drivers in the model are the costs associated with optical colonoscopy and the managed CCE-2 service. Based on NHS reference costs, an optical colonoscopy procedure is approximately £600, and this figure is similar to the results of a micro-costing exercise undertaken by the CCE-2 manufacturer. However, NHS National Procurement contract data indicated a cost of £[redacted], paid to outsourced providers of traditional optical colonoscopy procedures. In order to best gauge the likely cost impact of CCE-2, a mid-point estimate was agreed during discussions with SCOTCAP stakeholders involved in the business case. The SCOTCAP business case team (from National Services Scotland [NSS]) provided data on the implementation costs of CCE-2, which have also been included in the analysis.

Table 13: Cost estimates used in the analysis

Cost item	Unit cost	Source
Optical colonoscopy procedure	£900	Mid-point estimate based on NHS reference costs (and micro-costing) for optical colonoscopy and a quote from NHS National Procurement NHS reference costs (£575), Micro-costing (£[redacted]), NHS national procurement outsourcing cost (£[redacted])
Flexible sigmoidoscopy procedure	£450	Assumed approx. 50% of the cost of optical colonoscopy
CT scan	£166	Assumed approx. 18 % of the cost of optical colonoscopy (based on relative NHS England reference costs of CT scan and colonoscopy)
CCE-2 capsule service cost (includes reading/provision of results)	£[redacted] £[redacted] £[redacted]	Manufacturer (provider) (first 3 years) Assumed 5% discount in year 4 Assumed 10% discount in year 5
CCE-2 service implementation costs (Scotland)	£[redacted]	National services Scotland (NSS) estimate
CCE-2 service implementation costs (North)	£[redacted]	National services Scotland (NSS) estimate
Complications: Bleeding requiring hospitalisation	£474	A weighted average of HRG costs for non-elective short-stay for gastrointestinal bleeds with and without interventions
Complications: Colon perforation	£2,841	A weighted average of HRG costs for non-elective long-stay for gastrointestinal bleeds with interventions
Average travel reimbursement claim (Scotland)	£19	Derived based on ISD data and personal communication with NHS boards
Average travel reimbursement claim (North)	£73	Derived based on ISD data and personal communication with NHS boards
Average travel reimbursement claim (excluding north)	£4.55	Derived based on ISD data and personal communication with NHS boards

Data have been redacted where they are academic or commercial in confidence. All data were visible to the Council during their deliberations.

Results: per-pathway cost

The average cost of the optical colonoscopy diagnostic pathway was estimated to be £977 and £962 for surveillance and symptomatic patients respectively. This includes the procedure cost, complications, patient travel and accounts for the rate of subsequent tests due to incomplete initial optical colonoscopy. Costs were contained within the same calendar year to help ensure all included costs were relevant to the one patient journey. According to expert opinion, approximately 10% of performed optical colonoscopies would be incomplete and will require additional tests. The rates of repeat optical colonoscopies for the two patient groups (approx. 8% for surveillance and 6% for symptomatic) were derived from the latest ISD data on number of patients and procedures. It was assumed that the remaining patients requiring a follow-up test would undergo a CT scan.

The average cost of the CCE-2 pathway was £1,267 in the surveillance patient subgroup, and £1,099 in the symptomatic subgroup. This difference was largely due to the higher rate of follow-up testing associated with surveillance, particularly optical colonoscopies, compared with symptomatic patients in SCOTCAP. The cost of CCE-2 was fixed for the first three years but, in order to gauge the impact of future downward cost pressure, a 5% and 10% cost reduction was applied for subsequent years. These reductions would lead to CCE-2 diagnostic pathway costs of £1,235 and £1,203 respectively for surveillance patients, and £1,067 and £1,035 for symptomatic patients.

The results of the per-pathway analysis show that CCE-2 is associated with a small incremental cost for symptomatic patients (approx. £100), whilst the incremental cost for surveillance patients is higher (approx. £300). The higher cost associated with the CCE-2 pathway compared with the colonoscopy pathway owes to the fact that a substantial proportion of patients receiving CCE-2 who will also have to undergo subsequent optical colonoscopy, flexible sigmoidoscopy or a CT scan procedures. In other words, for these patients, the cost of CCE-2 is additional to the invasive procedure cost.

Results: aggregated cost analysis

Table 14 shows that introducing the CCE-2 service in the diagnostic pathway for surveillance patients will cost an additional £1,837,398 in year 1, £631,126 in year 2, £633,261 in year 3, £567,028 in year 4 and £500,339 in year 5 compared with current practice if the CCE-2 service is to be rolled out across Scotland.

In the symptomatic patient group (table 15), the introduction of CCE-2 across Scotland will cost an additional £2,464,230 in year 1, £1,260,078 in year 2, £1,264,340 in year 3, £896,859 in year 4 and £526,879 in year 5.

This analysis again demonstrates that the incremental per patient cost in the symptomatic patient group is substantially lower than the cost in the surveillance group.

Table 14: aggregated and incremental per-patient cost impact analysis base case results – surveillance patients

Budget impact (BI)	Year 1*	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£3,438,027	£3,449,655	£3,461,323	£3,473,031	£3,484,778
Roll out to all boards	£5,275,425	£4,080,781	£4,094,584	£4,040,058	£3,985,117
Net BI vs Do nothing (aggregate)	£1,837,398	£631,126	£633,261	£567,028	£500,339
Net BI vs Do nothing (per patient)	£522	£179	£179	£159	£140

** Year 1 costs include NSS-estimated service implementation costs. See years 2 onwards for budget impact with implementation costs removed.*

Table 15: aggregated and incremental per-patient cost impact analysis base case results – symptomatic patients

Budget impact (BI)	Year 1*	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£43,841,391	£43,989,679	£44,138,468	£44,287,760	£44,437,558
Roll out to all boards	£46,305,621	£45,249,757	£45,402,808	£45,184,620	£44,964,436
Net BI vs Do nothing (aggregate)	£2,464,230	£1,260,078	£1,264,340	£896,859	£526,879
Net BI vs Do nothing (per patient)	£54	£28	£28	£19	£11

** Year 1 costs include NSS-estimated service implementation costs. See years 2 onwards for budget impact with implementation costs removed.*

Sensitivity analysis

Sensitivity analysis demonstrated that using the upper cost estimate (£[redacted]) for optical colonoscopy, the comparative average costs of the colonoscopy and CCE-2 diagnostic pathways were £1,301 and £1,473 respectively for surveillance patients. In the symptomatic patient group, the proposed CCE-2 diagnostic pathway led to a relatively lower per-patient cost of £1,250 versus £1,281 for the colonoscopy pathway. Potential cost savings are more likely to be realised in the symptomatic group due to the lower rate of optical colonoscopies following CCE-2, compared with the surveillance patient group. The analysis illustrates that, the higher the cost of the displaced traditional pathway, the more likely CCE-2 is to be cost-saving. The impact of using those cost estimates in the aggregated cost analysis are presented in appendix 5 (tables 22 and 23).

The impact of using the lowest procedural cost (NHS England reference costs) was explored (tables 24 and 25). The weighted average of the procedural cost with and without biopsy is £575 for colonoscopy and £401 for flexible sigmoidoscopy. The NHS England reference cost of a CT scan is £106.

There were concerns about the accuracy of the number of surveillance patients included in the analysis - based on the high variation between health boards (ranging from 0.19% to 20.91%) reported by ISD. The overall number of surveillance patients in the analysis might be an underestimation. To address this uncertainty, results were calculated based on the distribution of surveillance and symptomatic patients as observed for NHS Grampian (20% surveillance and 80% symptomatic) and applied across Scotland (tables 26 and 27).

It is recognised that only a subset of the population who underwent further investigation in the SCOTCAP study would do so in clinical practice. It has been suggested that only patients with polyps greater than 9mm, those with 6-9mm polyps and inadequate bowel preparation, an incomplete test, or other pathology will be further investigated. If this becomes clinical practice, the current base case results overestimate the cost of implementing CCE in the diagnostic pathway. Aggregate and incremental per-patient cost impact results (shown in tables 28 and 29) show possible long term cost savings in the symptomatic patient group.

Conclusion

In assessing diagnostic accuracy of CCE-2, the best quality evidence remains the meta-analysis of five prospective diagnostic studies reported in Evidence Note 86. This systematic review and meta-analysis reported a per-patient sensitivity of 87% and a per-patient specificity of 76% for CCE-2 detecting clinically significant colorectal polyps (≥ 6 mm) in patients scheduled to undergo optical colonoscopy for known or suspected colonic disease and with positive findings from a screening programme test[7].

If the per-patient sensitivity and specificity from the meta-analysis are applied to a theoretical cohort of 1,000 people with a positive FIT 80 µg Hb/g faeces from the Scottish bowel screening programme, at a per-patient clinically relevant polyp prevalence rate of 39.69%[15], this would equate to:

- 345 true positives which receive an optical colonoscopy,
- 145 *false positives* who would have an unnecessary optical colonoscopy,
- 458 true negatives who would appropriately not receive further intervention and,
- 52 *false negatives* who should receive an optical colonoscopy but would not.

Using these data, CCE-2 has a positive predictive value (PPV) of 70% and negative predictive value (NPV) of 90%. This means that one in ten of all negative results from CCE-2 will be a false negative - someone with clinically significant polyps who should receive a follow-up colonoscopy for polyp excision but would not. If CCE-2 were applied in a population with a higher risk of colorectal cancer, and thus a higher polyp prevalence rate, then the NPV would decrease (more false negatives). For example, if the prevalence rate of polyps were 50%, the NPV would be 85% and if the prevalence rate were 60%, the NPV would be 80%.

No secondary evidence was available to address the diagnostic accuracy of CCE-2 in other patient populations, such as asymptomatic first-degree relatives of colorectal cancer patients, patients who have had an incomplete colonoscopy, surveillance patients, and patients unwilling or unable to receive an optical colonoscopy. The diagnostic accuracy measures used in the primary studies covering these populations varied, meaning that pooling of results would be inappropriate.

While there are potentially advantages to using CCE-2 in rural and community settings, this has only been explored by two published prospective cohort studies [21, 39] and one unpublished prospective cohort study (SCOTCAP). Only one of these studies provided diagnostic accuracy data[21]. The use of CCE-2 in a community setting should not affect diagnostic accuracy, however the diagnostic accuracy for a particular patient group should be considered alongside data on the feasibility of using CCE-2 in the community. All three prospective cohort studies demonstrated that the use of CCE-2 in a community or rural setting was feasible.

When comparing CCE-2 with CTC, the statistical significance of results varied between studies. This may have been due to differences between the studies in inclusion and exclusion criteria, measures of diagnostic accuracy, bowel cleansing regimes, and risk of bias. It therefore remains unclear, based upon current published evidence, whether CCE-2 would be a suitable alternative test for patients who currently receive CTC.

Studies exploring patient and public preferences relating to tests for colorectal polyps reported varying views. Views from the patient organisation consultation were based on feedback from the SCOTCAP project and focused around the need for clear information on the clinical need for CCE-2, the bowel cleansing regime, the possibility of a follow-up optical colonoscopy and the waiting time for results.

Adverse events associated with the CCE-2 technology continue to be reported in a small proportion of patients.

When considering the use of CCE-2 in an NHSScotland care pathway the impact of inadequate bowel cleansing on the efficacy of CCE-2 should be borne in mind. The majority of studies reported that a proportion of participants had inadequate bowel preparation and/or an incomplete colon examination using CCE-2. In a real-world setting these patients would then receive an optical colonoscopy as a follow-up.

The base-case findings in a *de novo* cost comparison analysis demonstrated that the introduction of CCE-2 as screening modality for optical colonoscopy may result in increased costs for NHSScotland. These results are highly sensitive to the costs of currently available procedures (optical colonoscopy, flexible sigmoidoscopy and CT scan). When these procedure costs are assumed to be at the higher end of the confidence interval, introducing CCE-2 in the symptomatic patient group could potentially be cost saving. Restricting invasive follow-up procedures to only those patients who meet certain clinical criteria (e.g. polyp size) or who have inadequate bowel preparation could improve the

likelihood of achieving long-term savings in the symptomatic patient group. The analysis shows that implementing CCE-2 in the symptomatic patient group is more likely to be cost-efficient than in the surveillance population.

Future work

The diagnostic accuracy evidence for CCE-2 detecting polyps in adults with signs or symptoms or at increased risk of colorectal cancer could be strengthened by a further meta-analysis that included data from primary studies that have been published since the meta-analysis published by Health Quality Ontario[7].

The full cost effectiveness of CCE-2 remains unknown. A registry which collects clinical outcome data would allow a cost effectiveness to be calculated in the future.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

About SHTG Recommendations

SHTG Recommendations are produced to inform a decision at a particular point in time and therefore are not routinely updated. This Recommendation will be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the development of SHTG Recommendations and how you can request a health technology assessment see, Healthcare Improvement Scotland website.

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

Acknowledgements

Reviewers

SHTG Executive would like to thank the following individuals who provided peer review comments on the draft review which were considered by the authors:

- Prof Susan Moug, Academic Colorectal Surgeon, NHS Greater Glasgow & Clyde
- Dr George Ramsay, Colorectal and General Surgeon, Aberdeen Royal Infirmary; Senior Lecturer, Aberdeen University
- Dr Chris Rodger, Colorectal Surgeon, NHS Forth Valley
- Dr Lisa Wilde, Head of Scotland and Northern Ireland, Bowel Cancer UK
- Prof Philip Wilson, Academic GP, Highlands

SHTG Executive would like to thank the following individuals and organisations of the Evidence Review Team who provided comments on the draft review which were considered by the authors:

- David Dunkley, Public Representative, Healthcare Improvement Scotland
- Dr Claudia Geue, Lecturer, Health Economics & Health Technology Assessment (HETA), Institute of Health & Wellbeing, Uni. Of Glasgow
- Prof Craig Ramsay, Acting Director of Health Services Research, Health Economics Research Unit, Uni. of Aberdeen
- Susan Siegel, Public Representative, Healthcare Improvement Scotland
- Dr Hester Ward, Consultant - Public Health Medicine, National Services Scotland

SHTG Executive would like to thank the following individuals and organisations who provided comments on the draft recommendation, which were considered by the SHTG Council:

- Susan Bishop, Head of Efficiency, Improvement & Innovation, NHS Forth Valley
- Prof Susan Moug, Academic Colorectal Surgeon, NHS Greater Glasgow & Clyde
- Noelle O'Neill, Public Health Scientist, NHS Highland
- Dr Chris Rodger, Colorectal Surgeon, NHS Forth Valley
- Sarah Smith, Head of Medical Sciences, NHS Lothian
- Prof Bob Steele, Senior research professor - colorectal cancer, University of Dundee
- Dr Lisa Wilde, Head of Scotland and Northern Ireland, Bowel Cancer UK

Declarations of interest were sought from all reviewers. Reviewers had no role in authorship or editorial control and the views expressed are those of HIS and the SHTG Council.

SHTG Council

SHTG Executive would like to thank the following individuals and organisations on the SHTG Council for developing this recommendation:

- Lynne Buttercase, North of Scotland Planning
- Ed Clifton, SHTG Unit Head, HIS
- Karen Facey, Evidence Based Health Policy Consultant
- Claire Fernie, Public Representative, Healthcare Improvement Scotland
- Rodolfo Hernandez, Health Economics Research Unit (HERU), University of Aberdeen
- Karen MacPherson, Lead Health Service Researcher, HIS
- Ralph Roberts, Chief Executive, NHS Borders
- Dr Iain Robertson, Council Chair, Consultant Interventional Radiologist, NHS GG&C
- Dr Neil Smart, Council Vice-Chair, Consultant Anaesthetist, NHS GG&C
- Hugh Stewart, Public Representative, Healthcare Improvement Scotland
- Ann Pullar, Senior Policy Manager – Health Technologies, Planning and Quality Directorate, Scottish Government
- Safia Qureshi, Director of Evidence, HIS

Healthcare Improvement Scotland development team

SHTG Executive would like to thank the following individuals for developing this health technology assessment:

- Evan Campbell, Lead Author/Health Services Researcher
- Maria Dimitrova, Health Economist
- Paul Herbert, Information Scientist
- Charis Miller, Information Scientist
- Tracey MacGann, Project Officer
- James Stewart, Public Involvement Advisor

Published Aug 2020

References

1. National Cancer Institute. NCI dictionary of cancer terms. 2018 [cited 2018 Apr 17]; Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms.
2. Dorland I, Newman WA. Dorland's illustrated medical dictionary. Philidelphia: WB Saunders Company; 2000.
3. NHS Choices. Bowel polyps [online]. 2017 [cited 15 Feb 2018]; Available from: https://www.nhs.uk/conditions/bowel-polyps/.
4. Patient.info. Faecal occult blood test [online]. 2017 [cited 2020 May 15]; Available from: https://patient.info/health/colon-rectal-bowel-cancer-colorectal/faecal-occult-blood-test.
5. Scottish Health Technologies Group. Colon capsule endoscopy (CCE-2) for the detection of colorectal polyps and cancer in adults with signs or symptoms of colorectal cancer or at increased risk of colorectal cancer. 2018 [cited 24 March 2020]; Available from: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/shtg_014-18.aspx.
6. Cancer Research UK. About bowel cancer [online]. 2015 [cited 15 Feb 2018]; Available from: http://www.cancerresearchuk.org/about-cancer/bowel-cancer/about-bowel-cancer.
7. Health Quality Ontario. Colon capsule endoscopy for the detection of colorectal polyps: an evidence-based analysis. 2015 [cited 2018 May 30]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561762/pdf/ohtas-15-1.pdf.
8. Cancer Research UK. Colonoscopy [online]. 2016 [cited 15 Feb 2018]; Available from: http://www.cancerresearchuk.org/about-cancer/cancer-in-general/tests/colonoscopy.
9. ECRI. PillCam COLON 2 capsule endoscopy system (Medtronic plc) for detecting colon polyps. 2017 [cited 12 Feb 2018]; Available from: https://www.ecri.org/components/ProductBriefs/Pages/14018.aspx?tab=2.
10. Negreanu L, Babiuc R, Bengus A, Sadagurschi R. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. World J Gastrointest Endosc. 2013;5(11):559-67.
11. Nogales O, Garcia-Lledo J, Lujan M, Nicolas D, Juanmartinena JF, Gonzalez-Suarez B*, et al.* Therapeutic impact of colon capsule endoscopy with PillCam (TM) COLON 2 after incomplete standard colonoscopy: a Spanish multicenter study. Rev Esp Enferm Dig. 2017;109(5):322-7.
12. Spada C, Hassan C, Campanale M, Costamagna G. Colon capsule endoscopy. Techniques Gastrointest Endosc. 2015;17(1):19-23.
13. SIGN. SIGN 126: diagnosis and management of colorectal cancer. 2011 [cited 9 Feb 2018]; Available from: https://www.sign.ac.uk/media/1064/sign126.pdf.
14. Spada C, Pasha SF, Gross SA, Leighton JA, Schnoll-Sussman F, Correale L*, et al.* Accuracy of first- and second-generation colon capsules in endoscopic detection of colorectal polyps: a systematic review and meta-analysis. Clinical Gastroenterol Hepatol. 2016;14(11):1533-43.
15. ISD Scotland. Scottish bowel screening programme: key performance indicators. 2020 [cited 27 February 2020]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/.
16. ISD Scotland. Cancer statistics: colorectal cancer. 2020 [cited 25 March 2020]; Available from: http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/Colorectal/.
17. Public Health Scotland. Bowel screening FIT test briefing sheer for professionals. 2017 [cited 1 July 2020]; Available from: http://www.healthscotland.scot/publications/scottish-bowel-screening-programme-a-guide-for-professionals.
18. Scottish Government. Coronavirus (COVID-19): guidance for use of FIT testing for patients with colorectal symptoms. 2020 [cited 2 July 2020]; Available from: https://www.gov.scot/publications/coronavirus-covid-19-guidance-for-use-of-fit-testing-for-patients-with-colorectal-symptoms/.
19. 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(2):570-5.

20. Adrian-de-Ganzo Z, Alarcon-Fernandez O, Ramos L, Gimeno-Garcia A, Alonso-Abreu I, Carrillo M*, et al.* Uptake of colon capsule endoscopy vs colonoscopy for screening relatives of patients with colorectal cancer. Clinical Gastroenterol Hepatol. 2015;13(13):2293-301.
21. Kobaek-Larsen M, Kroijer R, Dyrvig AK, Buijs MM, Steele RJC, Qvist N*, et al.* Back-to-back colon capsule endoscopy and optical colonoscopy in colorectal cancer screening individuals. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2018;20(6):479-85.
22. Parodi A, Vanbiervliet G, Hassan C, Hebuterne X, De Ceglie A, Filiberti RA*, et al.* Colon capsule endoscopy to screen for colorectal neoplasia in those with family histories of colorectal cancer. Gastrointest Endosc. 2017;87(3):695-704.
23. Spada C, Hassan C, Barbaro B, Iafrate F, Cesaro P, Petruzziello L*, et al.* Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial. Gut. 2015;64(2):272-81.
24. Baltes P, Bota M, Albert J, Philipper M, Horster HG, Hagenmuller F*, et al.* PillCamColon2 after incomplete colonoscopy - A prospective multicenter study. World J Gastroenterol. 2018;24(31):3556-66.
25. Hussey M, Holleran G, Stack R, Moran N, Tersaruolo C, McNamara D. Same-day colon capsule endoscopy is a viable means to assess unexplored colonic segments after incomplete colonoscopy in selected patients. United European Gastroenterol J. 2018;6(10):1556-62.
26. Kroijer R, Kobaek-Larsen M, Qvist N, Knudsen T, Baatrup G. Colon capsule endoscopy for colonic surveillance. Colorectal Dis. 2019;21(5):532-7.
27. Pecere S, Senore C, Hassan C, Riggi E, Segnan N, Pennazio M*, et al.* Accuracy of colon capsule endoscopy for advanced neoplasia. Gastrointest Endoscop. 2020;91(2):406.
28. Otani I, Oka S, Tanaka S, Iio S, Tsuboi A, Kunihara S*, et al.* Diagnostic yield of colon capsule endoscopy in detection of superficial colorectal lesions. Digestion. 2019:1-8.
29. Pioche M, Ganne C, Gincul R, De Leusse A, Marsot J, Balique J*, et al.* Colon capsule versus computed tomography colonography for colorectal cancer screening in patients with positive fecal occult blood test who refuse colonoscopy: a randomized trial. Endoscopy. 2018;50(8):761-9.
30. Kroijer R, Dyrvig AK, Kobaek-Larsen M, Stovring JO, Qvist N, Baatrup G. Booster medication to achieve capsule excretion in colon capsule endoscopy: A randomized controlled trial of three regimens. Endosc Int Open. 2018;6(11):E1363-E8.
31. Malaysian Health Technology Assessment (MaHTAS). Capsule endoscopy for colorectal cancer (CRC) screening. 2015 [cited 2018 May 30]; Available from: http://www.moh.gov.my/english.php/pages/view/199.
32. Spada C, Hassan C, Galmiche JP, Neuhaus H, Dumonceau JM, Alder S*, et al.* Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2012;44:527-36.
33. Yung DE, Plevris JN, Koulaouzidis A. Short article: Aspiration of capsule endoscopes: a comprehensive review of the existing literature. Eur J Gastroenterol Hepatol. 2017;29(4):428-34.
34. Imaeda A, Bender D, Fraenkel L. What is most important to patients when deciding about colorectal screening? J Gen Intern Med. 2010;25(7):688-93.
35. Rex DK, Lieberman DA. A survey of potential adherence to capsule colonoscopy in patients who have accepted or declined conventional colonoscopy. J Clin Gastroenterol. 2012;46(8):691-5.
36. Ojidu H, Palmer H, Lewandowski J, Hampton J, Blakeborough T, Epstein O*, et al.* Patient tolerance and acceptance of difference colonic imaging modalities: an observational cohort study. Eur J Gastroenterol Hepatol. 2018;30:520-5.
37. Thygesen MK, Baatrup G, Petersen C, Qvist N, Kroijer R, Kobaek-Larsen M. Screening individuals' experiences of colonoscopy and colon capsule endoscopy; a mixed methods study. Acta Oncol. 2019;58(Suppl1):S71-S6.
38. Palimaka S, Blackhouse G, Goeree R. Colon capsule endoscopy for the detection of colorectal polyps: an economic analysis. 2015 [cited 2018 May 30]; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4561761/pdf/ohtas-15-1.pdf.
39. Adler SN, Bjarnason I. What we have learned and what to expect from capsule endoscopy. World J Gastrointest Endosc. 2012;4(10):448-52.
40. Last J. A dictionary of epidemiology. 4th ed. New York: Oxford University Press; 2001.

Appendix 1: abbreviations

BI	budget impact
CCE	colon capsule endoscopy
CCE-2	PillCam™ Colon 2
CI	confidence interval
CT	computed tomography
CTC	computed tomographic colonography
FAQ	frequently asked questions
FIT	faecal immunochemical test
FOBT	faecal occult blood test
GCS	Gloucester Comfort Score
GP	general practitioner
KPI	key performance indicator
MaHTAS	Malaysian Health Technology Assessment
NPV	negative predictive value
OC	optical colonoscopy
OR	odds ratio
PPV	positive predictive value
RCT	randomised controlled trial
SD	standard deviation
SHTG	Scottish Health Technologies Group
SCOTCAP	Scottish Colon Capsule Project
VAS	visual analogue scale

Appendix 2: definitions of diagnostic accuracy terms

Sensitivity: the probability that a person having a disease will be correctly identified by a clinical test, that is the number of true positive results divided by the total number with the disease[40].

Specificity: the probability that a person not having a disease will be correctly identified by a clinical test, that is the number of true negative results divided by the total number of those without the disease[40].

Positive predictive value: probability that a person with a positive result has the disease, that is the number of true positives as a percentage of total positive results[40].

Negative predictive value: probability that person with a negative results does not have the disease, that is the number of true negatives as a percentage of total negative results[40].

Appendix 3: summary of clinical effectiveness literature from Evidence Note 86

Adults with a positive test for colorectal disease

A systematic review with meta-analysis of five studies (n=361) evaluated the diagnostic accuracy of CCE-2 (PillCam™ Colon 2) for detecting colorectal polyps in adults scheduled to undergo optical colonoscopy for known or suspected colorectal disease and positive findings from previous tests, such as bowel screening[7]. Four studies used optical colonoscopy as the reference standard, which was assumed to have perfect accuracy. The fifth study (Rondonotti et al, 2014) used a compound reference standard that integrated data from optical colonoscopy, CCE-2 and CT colonography. This reference standard was therefore at high risk of incorporation bias as the reference standard was not independent of the index tests. Endoscopists were blinded to CCE-2 results in the four studies using optical colonoscopy as the reference standard; the study with a compound reference standard used segmental unblinding during the optical colonoscopy (CCE-2 findings were revealed after optical colonoscopy examination of each section of colon). Based on the QUADAS-2 appraisal tool, four included studies were judged by the systematic review authors to be at high risk of selection and elimination bias as participants were not selected randomly or consecutively and not all participants were included in the analysis. If the characteristics of patients excluded from the study or not included in the analysis differ systematically from those included in the study this may have led to over-estimation of the diagnostic accuracy of CCE-2 in the meta-analysis. The bowel cleansing regimen used and the proportion of study participants with a complete CCE-2 examination were not reported for included studies.

The systematic review assessed the diagnostic accuracy of CCE-2 for detecting polyps ≥6mm, ≥10mm and of any size (table 16)[7]. Study participants had a mean age between 50 and 63 years (range 18 to 75) and 54% to 66% of patients were male. Overall CCE-2 had sensitivity ≥87% for detecting colorectal polyps. The lower specificity of CCE-2 for detecting polyps ≥6mm or of any size (76% and 75%, respectively) may be due to differences in polyp size estimation between CCE-2 and optical colonoscopy. Heterogeneity and uncertainty around the effect estimate was higher for analyses on polyps ≥6mm and polyps of any size. This was attributed by the review authors to between-study variation in efficacy of the bowel cleansing regimen used, however this assumption was not based on any sensitivity analyses. It should be noted that participants in the included studies agreed to undergo two or three colon examination procedures and therefore may not represent the real-world patient population.

Table 16: pooled diagnostic accuracy of CCE-2 for detection of colorectal polyps in a high-risk patient population[7]

	Polyps ≥6mm	Polyps ≥10mm	Polyps of any size
N studies	3	3	2
N patients	275	275	86
Pooled sensitivity (95% confidence interval (CI))	87% (77% to 93%)	89% (77% to 95%)	89% (66% to 97%)
Pooled specificity (95% CI)	76% (60% to 87%)	91% (86% to 95%)	75% (45% to 91%)

One study within the systematic review (Rondonotti et al, 2014) compared CCE-2 with CT colonography in 54 patients with a positive FOBT screening test who were offered optical colonoscopy[7]. Study participants had a mean age of 60 years (standard deviation (SD) 9 years) and 62% were male. This small study was at high risk of selection bias as patients were not recruited consecutively or randomly, high risk of bias from use of a compound standard, and high risk of elimination bias as not all participants were included in the analysis. These biases combined may have resulted in over-estimation of the diagnostic accuracy of CCE-2 and/or CT colonography in this study. No statistically significant differences in sensitivity or specificity were found between CCE-2 and CT colonography for the detection of polyps ≥6mm or ≥10mm (table 17).

Table 17: diagnostic accuracy of CCE-2 compared with CT colonography in patients with positive FOBT test results (n=54)[7]

	Polyps ≥6mm			Polyps ≥10mm		
	CCE-2	CT colonography	p-value	CCE-2	CT colonography	p-value
Sensitivity (95% CI)	88% (62% to 98%)	88% (62% to 98%)	0.99	93% (64% to 100%)	79% (49% to 94%)	0.26
Specificity (95% CI)	88% (71% to 96%)	85% (67% to 94%)	0.72	92% (76% to 98%)	92% (76% to 98%)	0.99

A prospective back-to-back study, published after the meta-analysis, assessed the use of CCE-2 (PillCam™ Colon 2) in 253 patients with a positive faecal immunochemical test (FIT)[21]. Participants were required to proactively contact the research team after receiving a letter about involvement in the study; this may have resulted in volunteer bias. Participants underwent CCE-2 followed by optical colonoscopy the next day allowing for use of a single bowel cleansing procedure. The bowel cleansing regimen included magnesium-oxide, water, Moviprep™, domperidone and rectal bisacodyl. The CCE-2 procedure was conducted at the patients' home with support from trained nurses which may have affected compliance rates. Clinicians performing optical colonoscopies were blinded to CCE-2 results. The reference standard was a combination of the initial optical colonoscopy, repeat

optical colonoscopies in patients with polyps detected on CCE-2 but not found on initial optical colonoscopy, and therapeutic colonoscopies to remove polyps. This reference standard was therefore at risk of incorporation bias which could result in overestimation of sensitivity.

Mean age of study participants was 64 years and 58% were male. The CCE-2 procedure completion rate was low (54%) possibly due to the lack of a potent booster in the bowel cleansing regimen[21]. Ninety percent of optical colonoscopy procedures were complete. Sensitivity and specificity of CCE-2 and optical colonoscopy for detection of polyps >9mm in all participants (n=253) and in participants that completed both tests (n=126) are reported in table 18. Both tests had good sensitivity and specificity for detection of polyps >9mm in patients with a positive bowel screening test. The polyp detection rate – proportion of all patients with at least one polyp detected – was statistically significantly higher for CCE-2 compared with optical colonoscopy in both the full patient group (74% versus 64%, p=0.02) and the subgroup with complete CCE-2 and optical colonoscopy examinations (86% versus 65%, p<0.001). CCE-2 also successfully detected seven out of eleven (64%) optical colonoscopy confirmed adenocarcinomas; the remaining four were missed due to incomplete CCE.

Table 18: diagnostic accuracy of CCE-2 and optical colonoscopy for detection of polyps >9mm in FIT-positive patients[21]

	All participants		Participants with two complete investigations	
	CCE-2	Optical colonoscopy	CCE-2	Optical colonoscopy
N patients	253		126	
Complete procedure (%)	54%	90%	-	-
Adequate bowel cleansing (%)	85%	95%	-	-
Sensitivity (95% CI)	87% (83% to 91%)	88% (84% to 92%)	97% (94% to 100%)	89% (84% to 94%)
Specificity (95% CI)	92% (89% to 95%)	100% (100% to 100%)	90% (85% to 95%)	100% (100% to 100%)

First-degree relatives of patients with colorectal cancer

Two prospective primary studies evaluated the use of CCE-2 for screening first-degree relatives of patients with colorectal cancer diagnoses[20, 22]. In the first study participants (n=177) underwent

CCE-2 examination followed by optical colonoscopy with polypectomy the next day[22]. People were excluded from the study if they had severe comorbidities, inflammatory bowel disease, familial adenomatous polyps, or hereditary non-polyposis colorectal cancer. Bowel cleansing for the CCE-2

procedure was more extensive than for optical colonoscopy: polyethylene glycol, metoclopramide, sodium phosphate, water and a bisacodyl suppository compared with a liquid diet and lower volume polyethylene glycol. A complete CCE-2 examination was defined as capsule excretion or visualisation of the anal verge, and a true positive was defined as detection of at least one polyp ≥6mm confirmed by optical colonoscopy. CCE-2 results were assessed by clinicians with prior experience of small bowel capsule endoscopy or first generation CCE. Endoscopists performing the optical colonoscopy were initially blinded to CCE-2 results and then un-blinded by colon segment so that the section could be re-examined for missed polyps.

All participants (100%) had complete CCE-2 and optical colonoscopy examinations. Bowel cleansing was adequate in 68% of participants for CCE-2 and 81% for optical colonoscopy. Participants had a mean age of 57 years (range 26 to 82 years) and 45% were male. Sensitivity and specificity of CCE-2 for detection of polyps ≥6mm and ≥10mm are presented in table 19. Fifty-six patients (32%) had polyps ≥6mm detected on optical colonoscopy. CCE-2 correctly identified 51 of the 56 polyps (91%) detected by optical colonoscopy.

Table 19: diagnostic accuracy of CCE-2 for the detection of colorectal polyps in first-degree relatives of colorectal cancer patients[22]

	Polyps ≥6mm	Polyps ≥10mm
Sensitivity (95% CI)	91% (81% to 96%)	89% (72% to 96%)
Specificity (95% CI)	88% (82% to 93%)	95% (90% to 97%)
Positive predictive value (PPV, 95% CI)	79% (67% to 87%)	75% (58% to 87%)
Negative predictive value (NPV, 95% CI)	96% (90% to 98%)	98% (94% to 99%)

The second study was described as a prospective pragmatic randomised open trial comparing screening uptake and detection rates for CCE-2 (PillCam™ Colon 2) and optical colonoscopy in asymptomatic first-degree relatives of patients with colorectal cancer[20]. Individuals were excluded from participating in the study if they had severe comorbidities or inflammatory bowel disease. Participants were initially randomly allocated to CCE-2 or optical colonoscopy using computer-generated number sequences and sealed envelopes. After randomisation participants could choose to swap to the alternative test which eliminated any benefit of the initial random allocation. The redistribution of participants between study groups and low recruitment mean that this study is underpowered to detect any difference in screening uptake based on the authors' power calculation. Participants in the CCE-2 group were referred for optical colonoscopy if they received a positive test result. A blinded independent observer reviewed CCE-2 results but it is unclear why this was necessary when participants only received one intervention.

Forty-five participants received CCE-2 and 81 had an optical colonoscopy. Twenty participants were receiving antiplatelet therapy and 68 had other chronic conditions. CCE-2 examination was complete in 67% of participants and optical colonoscopy in 82%; in both groups 80% of participants had adequate bowel cleansing. The study did not describe the bowel cleansing regimens used. Participants were statistically significantly more likely to swap to the optical colonoscopy group compared with changing to the CCE-2 group: odds ratio (OR) 3.11, 95% CI 1.51 to 6.41, p=0.002. Reasons for swapping to optical colonoscopy included avoiding a second procedure in the event of a positive result, greater confidence in optical colonoscopy and anecdotes of unpleasant experiences. The reason for declining optical colonoscopy was fear of the procedure. Fifty-six patients (44%) swapped group prior to testing. In an intention-to-screen analysis, where participants were analysed in the group they were originally randomised to, there was no statistically significant difference in screening uptake (OR 0.86, 95% CI 0.51 to 1.44, p=0.57). There were also no statistically significant differences in detection rates between CCE-2 and optical colonoscopy for clinically significant lesions or advanced adenomas in the intention-to-screen or as-screened analyses (table 20).

Table 20: CCE-2 and optical colonoscopy polyp detection rates in first-degree relatives of patients with colorectal cancer[20]

	Intention-to-screen		As-screened	
	Clinically significant lesions	Advanced adenoma	Clinically significant lesions	Advanced adenoma
Positive optical colonoscopy (n)	13	8	16	12
Optical colonoscopy detection rate (%)	11.5	7.1	19.8	14.8
Positive CCE-2 (n)	14	9	11	5
CCE-2 detection rate (%)	11.7	7.5	24.4	11.1
OR (95% CI)	1.02 (0.45 to 2.26) p=0.96	1.06 (0.39 to 2.86) p=0.92	1.31 (0.54 to 3.14) p=0.54	0.72 (0.23 to 2.19) p=0.56

Patients with incomplete optical colonoscopy

Two prospective cohort studies investigated the use of CCE-2 in patients with a previous incomplete optical colonoscopy[11, 23]. The first study compared CCE-2 (PillCam™ Colon 2) with CT colonography in 97 consecutively recruited patients[23]. Original indications for referral to optical colonoscopy included signs or symptoms of bowel disease (n=54), family history of colorectal cancer, or a positive FOBT test. Patients with chronic heart failure or renal insufficiency were excluded from the study. Patients with an incomplete optical colonoscopy due to inadequate bowel cleansing or colonic stricture, and

patients with polyps not removed at optical colonoscopy, were excluded; study results may therefore not generalise to these patient groups. Participants underwent CCE-2 and CT colonography on the same day after a single bowel cleansing procedure. The bowel cleansing procedure included water, Senna tablets, polyethylene glycol, sodium phosphate, a bisacodyl suppository and Gastrografin® tagging of faecal matter for CT colonography. Only patients with a positive result (one or more polyps ≥6mm) on either CCE-2 or CT colonography received an optical colonoscopy. Clinicians interpreting CCE-2 and CT colonography were blinded to previous test results.

Median age of participants was 59 years (range 33 to 75 years) and 34% were male. The completion rate for both CCE-2 (98%) and CT colonography (98%) was high in this study, which may be due to the definition used for procedure completion: visualisation of the colon section missed on the incomplete optical colonoscopy rather than visualisation of the entire colon. Bowel cleansing was adequate for 83% of participants for CCE-2 and 90% for CT colonography. As not all participants received a complete optical colonoscopy this study reported test performance as diagnostic yield, relative sensitivity and positive predictive values (Table 21). Diagnostic yield was described as the ratio between the number of patients with significant findings and overall number of patients tested. For detection of polyps ≥6mm CCE-2 was associated with a statistically significant two-fold increase in sensitivity compared with CT colonography. The difference in sensitivity was not statistically significant for polyps ≥10mm, possibly due to the low prevalence of this polyp size in study participants (n=6).

Table 21: performance of CCE-2 compared with CT colonography in patients with a previous incomplete optical colonoscopy[23]

	Polyps ≥6mm		Polyps ≥10mm	
	CCE-2	CT colonography	CCE-2	CT colonography
N patients	97		97	
N patients with confirmed polyps	24		6	
Relative sensitivity (95% CI)	2.0 (1.34 to 2.98) p<0.05		1.67 (0.69 to 4.00) NS	
Diagnostic yield (95% CI)	24.5% (16.6% to 34.4%)	12.2% (6.8% to 20.8%)	5.1% (1.9% to 12.1%)	3.1% (0.8% to 9.3%)
PPV (95% CI)	96% (77.7% to 99.8%)	85.7% (56.2% to 97.5%)	83.3% (36.5% to 99.1%)	100% (31.1% to 100%)

Diagnostic yield: ratio of patients with significant findings for each test to total number of patients

The second prospective cohort study in patients with incomplete optical colonoscopy reported the diagnostic yield for CCE-2 (PillCam™ Colon 2) in 96 consecutively recruited patients[11]. The reason for patient referral for optical colonoscopy was not reported and the definition of diagnostic yield was

not provided. Patients were excluded in they had chronic heart failure or moderate to severe renal or liver impairment. Procedure completion was defined as capsule expulsion or visualisation of the haemorrhoidal plexus and significant findings were defined as any polyp >6mm or more than three polyps of any size. Participants underwent bowel cleansing that included a clear liquid diet, polyethylene glycol, sodium phosphate, metoclopramide and a bisacodyl suppository. CCE-2 examination was complete in 69 participants (71.9%) and bowel cleansing was adequate for 74% of participants. Participants had a mean age of 58 years (SD 14.2) and 32% were male. CCE-2 identified all lesions detected on the incomplete optical colonoscopy plus additional lesions located in the colon section missed on optical colonoscopy (n=58, 60.4%). In 43 participants with additional lesions detected on CCE-2 the findings altered the therapeutic approach for that patient.

Patients unwilling or unable to undergo optical colonoscopy

One prospective cohort study was identified that examined the use of CCE-2 (PillCam™ Colon 2) in 70 patients at increased risk of colorectal cancer but unable or unwilling to undergo optical colonoscopy[10]. Participants had a personal or family history of colorectal disease, signs or symptoms, a positive FOBT test, or abnormal imaging test results, and had refused an optical colonoscopy (n=37), had an incomplete optical colonoscopy (n=30) or been contraindicated for optical colonoscopy due to anaesthetic risk or cardiovascular co-morbidities (n=3). As study participants did not receive an optical colonoscopy, CCE-2 findings were reported as the proportion of patients with clinically significant lesions (polyp >6mm or >3 polyps of any size) requiring medical or surgical intervention. Bowel preparation in this study involved only a clear liquid diet and polyethylene glycol due to local prescribing restrictions.

Forty-seven percent of participants were male and the mean age was 58 years (range 29 to 87 years). Bowel cleansing was adequate in 72% (n=48) of participants and 77% (n=54) completed the CCE-2 procedure within 12 hours. Clinically relevant lesions were detected in 23 patients (34%) of whom 17 agreed to have a therapeutic intervention. Six patients who previously refused optical colonoscopy agreed to the procedure following discussion of CCE-2 results and polypectomy was performed in all cases. Sixty-five participants (93%) agreed they would be willing to undergo CCE-2 examination in the future if necessary.

Out-of-clinic setting

A single-arm prospective pilot study evaluated the feasibility of providing CCE-2 colonic examination in an out-of-clinic/home setting in Israel[19]. Forty-one patients with known or suspected colonic disease and up to 40 minutes travel time to a clinic were consecutively recruited. Reasons for participants requiring colon examination included bowel screening (n=32), following up after a positive FOBT screening test (n=4) and other colorectal cancer risk factors (n=5). Bowel cleansing included a clear liquid diet, polyethylene glycol, metoclopramide, sodium phosphate, water and a bisacodyl suppository. Patients were discharged home 15 minutes after swallowing the CCE-2

capsule and the CCE-2 data recording device was programmed to alert patients to take additional boosters (metoclopramide, sodium phosphate and bisacodyl) to ensure capsule progression through the colon. Patients with significant findings – a polyp ≥6mm or three polyps of any size – were referred for optical colonoscopy.

Mean age of participants was 57 years (range 21 to 77) and 77% were male. Rates of CCE-2 procedure completion (88%) and adequate bowel cleansing (95%) were similar to those reported in studies performed in clinical settings. All participants complied with the CCE-2 procedure. Sixteen patients (39%) requested minor instruction clarifications during the procedure. Clinically significant lesions were identified in ten participants and confirmed by optical colonoscopy for nine (one participant was lost to follow-up).

Appendix 4: patient organisation submission from Bowel Cancer UK

Tell us about the sources you used to gather information for this submission.

The factual information on the condition is from our website. All of the medical content on our website is regularly updated. We involve healthcare professionals and researchers to check our information is accurate and up to date. More information on how we produce our information can be found here.

The information about what people want from the technology was obtained from the SCOTCAP Evaluation Report as well as anecdotal information from our own conversations with patients.

What is the health condition and how does it affect the day-to-day lives of patients and their carers?

People with suspected bowel cancer (or other bowel problems) may be referred for a colonoscopy as part of the diagnostic process. They may have been experiencing symptoms and referred by their GP, or they may have had blood in their bowel cancer screening test and been referred by the Bowel Screening Programme.

Some individuals who are at higher risk of bowel cancer may have regular surveillance colonoscopies to check for polyps or cancerous growths. People with the genetic condition Lynch syndrome or those with a family history may fall under this category for example.

Generally, during a colonoscopy, a long flexible tube with a bright light and a tiny camera on the end is inserted through the back passage and enables the doctor or nurse to get a clear view of the bowel lining. During the test, if the doctor sees anything that needs further investigation, photographs and samples (biopsies) can be taken. Simple polyps can be removed during a colonoscopy.

Prior to having a colonoscopy, patients must prepare by cleaning the bowel. When the bowel is cleaned out properly, there is a better chance of seeing the bowel wall clearly to spot any changes. Some types of bowel preparation leave people unable to be away from a toilet for long periods of time, which is not ideal if they have to travel a long distance to the hospital for their procedure or if they rely on public transport to travel there.

Although most people experience only minor discomfort during a colonoscopy, we know that some individuals find it painful and distressing. People whose bowels are already inflamed from the presence of another bowel condition, can find them particularly unpleasant.

Colonoscopies carry a very small risk of causing tears in the wall of the bowel.

What do patients and carers want from the health technology?

Some of the main things people want from the colon capsule are to reduce the amount of time waiting for a colonoscopy and to avoid a colonoscopy if they believe (or have previously experienced) that it may be uncomfortable.

Colonoscopy services are under pressure due to staff shortages and the demand for the service, so people are not always seen in a timely fashion. We know that waiting for medical tests can be an anxious time and particularly so if there is a suspicion of cancer. Being able to access a colon capsule test more quickly could help reduce some of this "waiting anxiety". It does need to be made clear to patients up front, however, that they may still need to go for a colonoscopy depending on the findings of the colon capsule. This will entail a further waiting period.

We also know that some people find colonoscopies uncomfortable or believe that they will be without having been through the procedures before. The colon capsule is perceived to be less invasive than a tradition colonoscopy, with less of the potential "embarrassment factor". As it simply a pill to be swallowed that will travel through the bowel patients feel that there is less likely to be the same pain and discomfort associated with the capsule as there might be with a traditional colonoscopy.

Convenience is a further expectation of the colon capsule, since it does not involve staying in hospital for any length of time and can be at least partially completed at home. As sedation is not needed, there is no requirement for a family member or friend to accompany the patient. We know that for some people who live alone or who do not have close family, it can be difficult to find someone to take them to or from to colonoscopy appointments, particularly if they are reluctant to ask a friend to assist. However, there was an expectation from some of the SCOTCAP participants that they would still be fairly mobile and active while the colon capsule was travelling through the body. This ended up not being the case for some participants as they felt the belt and holster were somewhat restrictive and awkward. It would be helpful to manage the expectations of people due to use the colon capsule in terms of how active they realistically might be while wearing the device, given their size and level of fitness or frailty.

The shorter distance to travel for some patients is a motivating factor for choosing the colon capsule over a traditional colonoscopy. For those individuals who live farther from a large hospital or who do not have easy access to a car, this could make a significant difference to their comfort levels in advance of the procedure.

It's not clear if patients would expect or appreciate that the bowel preparation is more rigorous for the colon capsule. Anecdotally from our own stakeholders we know that many people find the bowel preparation more unpleasant than the colonoscopy itself, and the comments in the SCOTCAP Evaluation Report reflect this, with many people commenting negatively on the experience. As this is also an often commented on aspect of colonoscopy, this probably reflects more generally on the

difficulty of getting a tolerable bowel preparation both in terms of volumes of liquid patients are required to ingest but also the potential for discomfort. For those participants who had experienced bowel preparation for a colonoscopy previously, they did feel this was worse for the colon capsule and for some it impacted more on their ability to work and carry out daily activity than anticipated.

It is not clear what patients' expectations are in terms of possible risks from the colon capsule versus a colonoscopy.

There appeared to be a lack of clarity for a small minority of patients around how long it would take to receive test results. It's unclear from the report if this is representative of the larger group who participated but details about time to wait for results should be made clear in both printed materials and face to face or phone conversations about the procedure.

What difference did the health technology make to the lives of patients that have used it? (Leave blank if you didn't make contact with anyone who had experience of the health technology.)

(section left blank)

Additional information you believe would be helpful for SHTG to consider.

It was clear from the SCOTCAP evaluation (and anecdotally from patients we are in contact with) that clear information and communication is key to avoid confusion and build confidence in the technology and this new pathway.

The invitation letter needs to be clear about why colon capsule is being offered rather than a full colonoscopy and that, depending on the outcome, some people may still need to go for a colonoscopy.

If the technology is adopted into use, and as it becomes clear what the areas are that cause confusion or concern, additional guidance could be developed such as the FAQ's suggested by one of the SCOTCAP participants which may over time reduce the demand on any phone support. This should be provided in a range of mediums – written/electronic/apps etc. given the wide age range and technological abilities of potential users. Videos giving a general, plain English explanation of the technology and what to expect may be useful.

Similarly, there appeared to be a need for a greater amount of information about what happens between swallowing the capsule, such as what buttons to press on the external device and what happens if it makes a noise, through to giving realistic timescales for results to be returned. Waiting for test results can be an anxious time for many so being clear about how long this might take, and being able to stick to those timetables is important.

It's not clear what choice patients will have in terms of colon capsule versus colonoscopy once this becomes part of the pathway. From the SCOTCAP evaluation, it seems that some of the participants, had they realised they might still have to go for a colonoscopy anyway would have opted to wait and go for the colonoscopy. Will there be an option for patients to choose to wait in this way? Or will they have to have the colon capsule unless there is some contraindication?

Please summarise the key points of your submission in up to 5 statements.

- Communication with patients needs to be very clear in setting out why they are being offered colon capsule, that they may still need a colonoscopy at a later date, and what they can expect from the procedure.
- Patients need to understand the timelines for getting results. Be realistic about what can be achieved given the potential for staff holiday/absence. Bear in mind waiting for results in this way causes anxiety for many.
- The bowel preparation required for colon capsule can be a very unpleasant process for some people. This may cause additional difficulties if they have a long way to travel to the hospital/GP or if they have to use public transport.

Appendix 5: de novo costing analysis based on SCOTCAP - results from sensitivity analyses

Table 22: aggregated and incremental per-patient cost impact analysis results for surveillance patients – highest procedural cost for current pathway (i.e. using National Procurement outsourcing cost of colonoscopy)

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£4,579,833	£4,595,323	£4,610,867	£4,626,462	£4,642,111
Roll out to North region only	£5,198,342	£4,724,861	£4,741,770	£4,737,290	£4,732,265
Net BI vs Do nothing (aggregate)	£618,509	£129,538	£130,904	£110,828	£90,154
Net BI vs Do nothing (per patient)	£578	£119	£119	£99	£80
Roll out to all boards	£6,176,683	£4,985,088	£5,001,949	£4,950,492	£4,898,631
Net BI vs Do nothing (aggregate)	£1,596,850	£389,764	£391,082	£324,030	£256,520
Net BI vs Do nothing (per patient)	£454	£110	£110	£91	£72

Table 23: aggregated and incremental per-patient cost impact analysis results for symptomatic patients – highest procedural cost for current pathway (i.e. using National Procurement outsourcing cost of colonoscopy)

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£58,401,682	£58,599,218	£58,797,422	£58,996,296	£59,195,843
Roll out to North region only	£58,738,015	£58,445,401	£58,643,786	£58,765,259	£58,885,190
Net BI vs Do nothing (aggregate)	£336,333	-£153,817	-£153,636	-£231,037	-£310,654
Net BI vs Do nothing (per patient)	£37	-£16	-£16	-£24	-£32
Roll out to all boards	£58,840,112	£57,826,643	£58,022,234	£57,846,729	£57,669,374
Net BI vs Do nothing (aggregate)	£438,429	-£772,575	-£775,188	-£1,149,567	-£1,526,470
Net BI vs Do nothing (per patient)	£10	-£17	-£17	-£25	-£33

Table 24: aggregated and incremental per-patient cost impact analysis results for surveillance patients – lowest procedural cost for current pathway (i.e. using NHS England reference costs)

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£2,205,379	£2,212,838	£2,220,323	£2,227,833	£2,235,368
Roll out to North region only	£2,981,732	£2,502,749	£2,514,165	£2,504,202	£2,493,705
Net BI vs Do nothing (aggregate)	£776,353	£289,910	£293,842	£276,370	£258,337
Net BI vs Do nothing (per patient)	£726	£267	£267	£248	£228
Roll out to all boards	£4,333,378	£3,135,547	£3,146,153	£3,088,419	£3,030,259
Net BI vs Do nothing (aggregate)	£2,127,999	£922,709	£925,830	£860,587	£794,891
Net BI vs Do nothing (per patient)	£604	£261	£261	£242	£223

Table 25: aggregated and incremental per-patient cost impact analysis results for symptomatic patients – lowest procedural cost for current pathway (i.e. using NHS England reference costs)

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£28,122,691	£28,217,812	£28,313,255	£28,409,021	£28,505,111
Roll out to North region only	£29,394,216	£29,011,444	£29,119,496	£29,150,463	£29,179,716
Net BI vs Do nothing (aggregate)	£1,271,525	£793,632	£806,241	£741,442	£674,605
Net BI vs Do nothing (per patient)	£138	£85	£85	£77	£69
Roll out to all boards	£33,110,721	£32,010,227	£32,118,497	£31,855,376	£31,590,109
Net BI vs Do nothing (aggregate)	£4,988,030	£3,792,414	£3,805,242	£3,446,355	£3,084,998
Net BI vs Do nothing (per patient)	£109	£83	£83	£75	£67

Table 26: aggregated and incremental per-patient cost impact analysis - surveillance patients approximately 20% of all colonoscopy patients (NHS Grampian) vs 7% in base case

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£9,377,489	£9,409,207	£9,441,033	£9,472,966	£9,505,007
Roll out to North region only	£10,271,026	£9,817,217	£9,853,900	£9,850,426	£9,845,970
Net BI vs Do nothing (aggregate)	£893,536	£408,009	£412,868	£377,460	£340,963
Net BI vs Do nothing (per patient)	£445	£200	£200	£180	£160
Roll out to all boards	£12,301,532	£11,130,653	£11,168,301	£11,019,578	£10,869,722
Net BI vs Do nothing (aggregate)	£2,924,043	£1,721,446	£1,727,269	£1,546,613	£1,364,715
Net BI vs Do nothing (per patient)	£305	£179	£179	£159	£140

Table 27: aggregated and incremental per-patient cost impact analysis - symptomatic patients - approximately 80% of all colonoscopy patients (NHS Grampian) vs 7% in base case

Budget impact (BI)	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£37,990,669	£38,119,167	£38,248,100	£38,377,469	£38,507,276
Roll out to North region only	£38,722,321	£38,365,541	£38,499,592	£38,564,491	£38,627,910
Net BI vs Do nothing (aggregate)	£731,652	£246,373	£251,491	£187,022	£120,634
Net BI vs Do nothing (per patient)	£89	£29	£30	£22	£14
Roll out to all boards	£40,287,306	£39,211,085	£39,343,712	£39,154,641	£38,963,842
Net BI vs Do nothing (aggregate)	£2,296,637	£1,091,918	£1,095,611	£777,172	£456,566
Net BI vs Do nothing (per patient)	£58	£28	£28	£19	£11

Table 28: aggregated and incremental per-patient cost impact analysis - surveillance patients- hypothetical data on reduced follow-up rate of invasive procedures

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£3,438,027	£3,449,655	£3,461,323	£3,473,031	£3,484,778
Roll out to North region only	£4,028,718	£3,551,103	£3,563,861	£3,555,213	£3,546,004
Net BI vs Do nothing (aggregate)	£590,691	£101,447	£102,538	£82,183	£61,226
Net BI vs Do nothing (per patient)	£552	£94	£93	£74	£54
Roll out to all boards	£4,942,452	£3,746,682	£3,759,355	£3,703,695	£3,647,616
Net BI vs Do nothing (aggregate)	£1,504,426	£297,027	£298,032	£230,665	£162,839
Net BI vs Do nothing (per patient)	£427	£84	£84	£65	£46

Table 29: aggregated and incremental per-patient cost impact analysis - symptomatic patients- hypothetical data on reduced follow-up rate of invasive procedures

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Do nothing (current pathway)	£43,841,391	£43,989,679	£44,138,468	£44,287,760	£44,437,558
Roll out to North region only	£44,420,524	£44,081,587	£44,233,522	£44,308,420	£44,381,647
Net BI vs Do nothing (aggregate)	£579,133	£91,909	£95,055	£20,659	-£55,910
Net BI vs Do nothing (per patient)	£63	£10	£10	£2	-£6
Roll out to all boards	£45,457,462	£44,398,729	£44,548,901	£44,327,825	£44,104,743
Net BI vs Do nothing (aggregate)	£1,616,071	£409,050	£410,433	£40,065	-£332,814
Net BI vs Do nothing (per patient)	£35	£9	£9	£1	-£7