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In response to enquiry from the Scaling Digital Innovation Service

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## What is the clinical and cost-effectiveness of second generation colon capsule endoscopy (CCE-2) compared with optical colonoscopy or CT colonography for the detection of colorectal polyps and cancer in adults with signs or symptoms of colorectal cancer or at increased risk of colorectal cancer?

### What is an evidence note?

Evidence notes are rapid reviews of clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

### Key points

- A systematic review of five diagnostic accuracy studies (n=361) in patients scheduled to undergo optical colonoscopy for known or suspected colorectal disease reported that second generation colon capsule endoscopy (CCE-2) had 87% sensitivity and 76% specificity for detection of clinically significant colorectal polyps  $\geq 6$ mm. Included studies used optical colonoscopy as the reference standard and may have overestimated the diagnostic accuracy of CCE-2 due to selection and elimination bias.
- A prospective diagnostic cohort study (n=97) reported a statistically significant two-fold increase in relative sensitivity of CCE-2 compared with CT colonography for detection of colorectal polyps  $\geq 6$ mm in patients with prior incomplete optical colonoscopy. Another

prospective diagnostic cohort study (n=54) comparing CCE-2 with CT colonography in patients with a positive FOBT screening test found no statistically significant differences in sensitivity or specificity for detection of polyps  $\geq 6\text{mm}$  or  $\geq 10\text{mm}$ . This second study was at high risk of selection, incorporation and elimination bias.

- Prospective diagnostic cohort studies reporting on the use of CCE-2 in patients with an incomplete optical colonoscopy, unable to have an optical colonoscopy, or unwilling to have an optical colonoscopy, were limited to describing diagnostic yield and number of clinically significant lesions as participants did not receive the reference standard test (optical colonoscopy).
- In a small prospective cohort study (n=41) in patients living in remote areas, performing CCE-2 at home was feasible and detected clinically significant lesions that were confirmed by optical colonoscopy.
- A UK cross-sectional study found that patients undergoing CCE-2 (n=56), CT colonography (n=158) or optical colonoscopy (n=253) rated CCE-2 and CT colonography more highly than optical colonoscopy for overall tolerability. CT colonography was also rated more highly than CCE-2. Among members of the public (n=100) provided with information about each test, 45% stated that they would choose optical colonoscopy, 37% CT colonography and 18% CCE-2 for investigating bowel symptoms.
- Studies reported colon capsule retention in 0.8% (95% CI 0.2% to 2.4%), and capsule aspiration in 0.1%, of people tested. Capsule retention or aspiration may require intervention to retrieve the capsule.

## Definitions

Definitions of terms relating to diagnostic test accuracy are provided in appendix 1.

**Adenoma:** a type of bowel/colorectal polyp that may develop into cancer if not removed<sup>1</sup>.

**Anal verge:** the end of the anal canal where the anal wall meets the external skin<sup>2</sup>.

**Bowel/colorectal polyps:** small abnormal tissue growths in the inner lining of the colon or rectum<sup>3</sup>.

**Haemorrhoidal plexus:** a network of veins that surround the lower part of the rectum<sup>2</sup>.

**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<sup>4</sup>.

A list of abbreviations used in this evidence note are provided in appendix 2.

## Literature search

A systematic search of the secondary literature was carried out between 9 and 12 February 2018 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.

A search of the primary literature was conducted to identify studies that explored the diagnostic accuracy of colon capsule endoscopy (CCE) in specific groups of patients not included in the secondary evidence. The primary literature was systematically searched between 9 and 12 February 2018 using the following databases: Medline, Medline in process, Embase, Cinahl and Web of Science.

A search was carried out on 16 April 2018 to identify literature on patient experiences and preferences relating to CCE and other colon imaging tests to inform the patient and social aspects section of the evidence note. The Medline, Medline in process, and Cinahl databases were searched.

All search results were limited to English language and studies published since 2009 (date when second generation PillCam™ Colon was launched).

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 metres of the large intestine<sup>5</sup>. 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<sup>6</sup>. People in Scotland with signs or symptoms of colorectal polyps or cancer, or with a positive bowel screening test, are currently referred for an optical colonoscopy.

Optical colonoscopy is an outpatient procedure that allows clinicians to examine the inside of the colon<sup>7</sup>. 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 projected onto 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<sup>8</sup>. However, in approximately 5% to 20% of patients referred for optical colonoscopy, the procedure cannot be completed<sup>9,10</sup>. This may be due to poor adherence to the bowel cleansing regimen, unusual anatomy

obstructing the colonoscope, or patient intolerance of the procedure<sup>8, 11</sup>. In addition, 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 (CT) colonography instead (Dr K Moffat, Medical Advisor, National Services Scotland. Personal communication, 1 February 2018). Frail elderly patients could also be unable to undergo optical colonoscopy due to the bowel cleansing required and may therefore have a CT colonography<sup>12</sup>. CT colonography allows colon examination by producing a 3D reconstruction of the inside of the colon using CT imaging<sup>8</sup>. The procedure is quick, taking only a few seconds, however 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 new non-invasive technique for examining the colon using a small capsule containing one or more cameras. CCE does not involve sedation, patient exposure to ionising radiation or air insufflation of the colon<sup>11</sup>. However, unlike optical colonoscopy it is not possible to biopsy or remove suspicious polyps during the CCE procedure. Potentially CCE could be used to detect 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 CT colonography, or as an initial investigation in patients referred for optical colonoscopy.

Optical colonoscopy, CT colonography 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 CT colonography. 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 evidence note which focused on the effectiveness of the CCE device. However it is likely that the diagnostic accuracy of all three tests, CCE, optical colonoscopy and CT colonography, will depend on the effectiveness of the bowel cleansing regimen performed.

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 evidence note.

## Health technology description

A first-generation PillCam™ Colon was replaced with the second-generation PillCam™ Colon 2 in 2009. In PillCam™ Colon 2 the camera frame rate and angle of view have been increased and the data recorder procedure simplified<sup>13</sup>. This review only considers evidence on second-generation CCE (CCE-2).

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<sup>8, 11</sup>. PillCam™ Colon 2 (Medtronic plc, Dublin, Ireland) is a second-generation colon capsule endoscope and the main colon capsule technology currently on the market in the UK. The PillCam™ Colon 2 capsule measures 11.6mm by 31.5mm and 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 (LEDs) to illuminate the area around the cameras and bidirectional wireless communication technology. The cameras have an adaptive frame rate which allows the PillCam™ Colon 2 to take more images when moving through the colon and fewer images when stationary or in other parts of the body (35 images/s versus 4 images/s).

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<sup>8, 11</sup>. 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<sup>11</sup>. A typical bowel cleansing regimen for CCE-2 involves ingesting four litres of polyethylene-glycol (PEG) 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.

CCE-2 transit through the digestive system takes up to ten hours depending on the individual. The capsule can be swallowed at a community health facility and the patient can return home after successfully ingesting the capsule<sup>8</sup>. 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 PillCam™ Colon 2 which converts images into time-compressed video format for easier viewing<sup>8, 11</sup>. Reading and interpretation of CCE-2 images requires skilled personnel and can be outsourced to non-NHS organisations that specialise in CCE-2 image interpretation.

Colon capsule endoscopy is not currently used in routine practice in Scotland. Proposed indications for use from the manufacturer of PillCam™ Colon 2 include 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<sup>3</sup>. Most colorectal polyps are not malignant, but if polyps are not removed they can eventually become cancerous. A polyp  $\geq 6$ mm or three polyps of any size are considered clinically significant and polyps  $\geq 10$ mm are associated with advanced adenoma<sup>6</sup>. Most colorectal cancers develop from precancerous polyps<sup>6, 14</sup>.

Colorectal cancer is more common in people aged over 50, with approximately 95% of colorectal cancer diagnoses in this age group<sup>15</sup>. 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<sup>6</sup>.



Colorectal cancer is the third most common cancer in Scotland with 3,671 new diagnoses in 2015 and 1,565 people dying from the disease in the same year<sup>15</sup>. 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<sup>14</sup>. Seventy-eight percent of patients referred for optical colonoscopy following a positive screening test between 1 May 2015 and 30 April 2017 attended for the procedure. The rate of incomplete optical colonoscopy (4.5%) and complications following optical colonoscopy (0.5%) were low. It should be noted however that less than 60% 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 May 2015 and 30 April 2017 inclusive**

	<b>Positive screening test*, n</b>	<b>Colonoscopies performed, n (%)</b>	<b>Incomplete colonoscopies, n (%)</b>	<b>Complications following optical colonoscopy**, n (%)</b>
<b>Male</b>	12,085	9,546 (79.0)	302 (3.2)	59 (0.6)
<b>Female</b>	9,465	7,345 (77.6)	456 (6.2)	22 (0.3)
<b>All persons</b>	21,550	16,891 (78.4)	758 (4.5)	81 (0.5)

*\*The bowel screening test in Scotland has changed from gFOBt to FIT since these data were collected*

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

## Clinical effectiveness

Both false positive and false negative results from colon examination have negative implications. People receiving a false positive result may be subjected to unnecessary medical procedures, usually optical colonoscopy, with all the attendant risks. When someone is given a false negative result the individual is at risk of progressing to colorectal cancer before being correctly diagnosed. Therefore tests with high sensitivity for detecting clinically relevant colorectal polyps are likely to be desirable.

The evidence base for CCE-2 in detecting colorectal polyps/cancer consisted of one systematic review with meta-analysis<sup>6</sup> and seven primary studies not included in the meta-analysis as they related to different patient populations or were published after the review inclusion period<sup>9, 10, 16-20</sup>.

As mentioned in the introduction, optical colonoscopy is the reference standard for colon examination and is therefore needed to calculate diagnostic accuracy measures such as sensitivity and specificity<sup>8</sup>. Several of the populations of interest to this evidence note are, by definition, unable or unwilling to have an optical colonoscopy. Consequently five primary studies reported alternative measures of diagnostic performance, such as diagnostic yield or detection rate.

Studies included in the evidence note used similar definitions of clinically significant colorectal polyps and recruited participants with indications for optical colonoscopy applicable to the Scottish context.

There was more between-study variation in the proportion of study participants with a complete colon examination and adequate bowel cleansing for CCE-2 groups (54% to 100% and 68% to 95% respectively) compared with optical colonoscopy groups (82% to 100% and 80% to 95%, respectively). This variation in complete examination and adequate bowel preparation rates is likely to have affected estimated of the diagnostic accuracy of CCE-2 in the studies.

### *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<sup>6</sup>. 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  $\geq 6\text{mm}$ ,  $\geq 10\text{mm}$  and of any size (table 2)<sup>6</sup>. 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  $\geq 87\%$  for detecting colorectal polyps. The lower specificity of CCE-2 for detecting polyps  $\geq 6\text{mm}$  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  $\geq 6\text{mm}$  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 2: pooled diagnostic accuracy of CCE-2 for detection of colorectal polyps in a high-risk patient population<sup>6</sup>

	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<sup>6</sup>. 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 3).

Table 3: diagnostic accuracy of CCE-2 compared with CT colonography in patients with positive FOBT test results (n=54)<sup>6</sup>

	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)<sup>18</sup>. 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<sup>18</sup>. 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 4. 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 4: diagnostic accuracy of CCE-2 and optical colonoscopy for detection of polyps >9mm in FIT-positive patients<sup>18</sup>

	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<sup>17, 19</sup>. In the first study participants (n=177) underwent CCE-2 examination followed by optical colonoscopy with polypectomy the next day<sup>19</sup>. 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  $\geq 6\text{mm}$  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 unblinded 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  $\geq 6\text{mm}$  and  $\geq 10\text{mm}$  are presented in table 5. Fifty-six patients (32%) had polyps  $\geq 6\text{mm}$  detected on optical colonoscopy. CCE-2 correctly identified 51 of the 56 polyps (91%) detected by optical colonoscopy.

Table 5: diagnostic accuracy of CCE-2 for the detection of colorectal polyps in first-degree relatives of colorectal cancer patients<sup>19</sup>

	Polyps $\geq 6\text{mm}$	Polyps $\geq 10\text{mm}$
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<sup>17</sup>. 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 6).

Table 6: CCE-2 and optical colonoscopy polyp detection rates in first-degree relatives of patients with colorectal cancer<sup>17</sup>

	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<sup>10, 20</sup>. The first study compared CCE-2 (PillCam™ Colon 2) with CT colonography in 97 consecutively recruited patients<sup>20</sup>. 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 7). 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  $\geq 6\text{mm}$  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  $\geq 10\text{mm}$ , possibly due to the low prevalence of this polyp size in study participants (n=6).

Table 7: performance of CCE-2 compared with CT colonography in patients with a previous incomplete optical colonoscopy<sup>20</sup>

	Polyps $\geq 6\text{mm}$		Polyps $\geq 10\text{mm}$	
	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<sup>10</sup>. 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  $>6\text{mm}$  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<sup>9</sup>. 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<sup>16</sup>. 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).



## Ongoing research

Following a feasibility study (HICAP) which explored community-based CCE-2 in rural parts of the Scottish Highlands, several Scottish research projects on CCE-2 have been commissioned by the Digital Health & Care Institute. Research projects that are currently in progress or recently completed include a cost analysis by the University of Strathclyde, an evaluation project by the universities of Aberdeen and Strathclyde, and a graphical summary of patient experiences of CCE-2 in Scotland. For further details about ongoing research on CCE-2 in Scotland see appendix 3.

A table of registered ongoing studies on CCE-2 for detecting colorectal polyps/cancer in patient populations of interest to this evidence note is provided in appendix 3. Three ongoing studies are located in Europe and four in Japan. In those studies that include a comparison between colon imaging techniques, two compare CCE-2 with CT colonography and two compare CCE-2 with optical colonoscopy.

## Patient and social aspects

Four primary studies were identified that explored patient experiences and preferences relating to colon capsule endoscopy and other colon imaging technologies<sup>19, 21-23</sup>. One study conducted in the UK explored tolerance and acceptability of optical colonoscopy, CT colonography and CCE-2 for colon examination<sup>23</sup>. Consecutive patients undergoing optical colonoscopy for symptoms (n=158), optical colonoscopy following referral from the national bowel screening programme (n=77), CT colonography (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 8. Median age of patients was lower for CCE-2 than other groups and highest in the CT colonography group. Approximately 29% of patients undergoing CT colonography and 21% of patients receiving CCE-2 had previously had an incomplete optical colonoscopy. Eighteen percent of patients having CT colonography 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 CT colonography or CCE-2 ( $p < 0.001$ ). Overall patient tolerability of the procedure (VAS score) was statistically significantly better for CT colonography and CCE-2 compared with optical colonoscopy ( $p < 0.001$ ); CT colonography 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 8: patient tolerance and acceptability of optical colonoscopy, CT colonography and CCE-2<sup>24</sup>

	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 CT colonography 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.

The three other studies explored patient aspects relating to CCE-2 as a bowel screening test<sup>19, 21, 22</sup>:

- One study in first-degree relatives of patients with colorectal cancer (n=177), previously described in the clinical effectiveness section, evaluated participant satisfaction with CCE-2 and optical colonoscopy as a secondary outcome<sup>19</sup>. 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)<sup>21</sup>. 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 CT colonography and 23% selected CCE-2.
- The third study was a market research survey in screening-eligible, paid volunteers (n=308)<sup>22</sup>. 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.

## Safety

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<sup>25</sup>. In addition 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 medical devices; patients with swallowing disorders; and pregnant women<sup>25, 26</sup>. 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<sup>25</sup>.

Two systematic reviews were identified that reported on adverse event rates for colon capsule endoscopy<sup>6, 27</sup>. The systematic review with meta-analysis discussed in the clinical effectiveness section reported adverse events relating to CCE-2, CT colonography and optical colonoscopy<sup>6</sup>. 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 CT colonography 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<sup>27</sup>. 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 ( $78.9\pm 7.8$  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%.

## Cost effectiveness

A primary economic analysis was identified that assessed the cost-effectiveness of providing CCE-2 as an alternative to CT colonography in patients with known or suspected colonic disease and a positive finding from a previous test in Ontario, Canada<sup>28</sup>. 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<sup>6</sup>. 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)<sup>6</sup>. Details of the analysis are therefore not reported.

## Conclusion

When considering the diagnostic accuracy of CCE-2, issues that must be borne in mind include the need for adequate bowel preparation, the proportion of study participants with complete colon examination and the skills required to effectively interpret images produced by the CCE-2 device. The majority of studies in this evidence note reported that a proportion of participants had inadequate bowel preparation and/or an incomplete colon examination using CCE-2. The review and interpretation of images from the CCE-2 test was also conducted by individuals with different backgrounds and levels of experience. Consequently the diagnostic accuracy estimates reported are likely to change in response to variation in the adequacy of bowel preparation, the number of complete colon examinations that are feasible and the experience of staff in interpreting CCE-2 images.

The best quality evidence consisted of a systematic review of five prospective diagnostic studies that considered the diagnostic accuracy of CCE-2 in patients scheduled to undergo optical colonoscopy for known or suspected colonic disease and with positive findings on a previous test. This systematic review reported 89% sensitivity and 76% specificity for CCE-2 detection of clinically significant colorectal polyps ( $\geq 6$ mm). However, the sensitivity and specificity of CCE-2 may have been over-estimated due to the risk of bias in included studies. The sensitivity of 89% indicates that CCE-2 may miss eleven cases of clinically significant bowel polyps for every 100 patients tested, which may be unacceptable in a clinical context.



No evidence syntheses were available to address the diagnostic accuracy of CCE-2 in other patient populations, including patients with a prior incomplete optical colonoscopy and patients unwilling or unable to have an optical colonoscopy. A number of prospective primary studies were identified, however these studies were limited to reporting detection rates or number of lesions identified as participants could not or would not have the reference standard test (optical colonoscopy) and therefore sensitivity and specificity could not be calculated. For this reason it is unlikely that the evidence on the diagnostic accuracy of CCE-2 in patients with incomplete colonoscopy, unable to have a colonoscopy or unwilling to undergo colonoscopy will improve in future.

In comparisons of CCE-2 with CT colonography the statistical significance of results varied between studies. This may be due to between-study differences in participant inclusion and exclusion criteria, measures of diagnostic accuracy used, bowel cleansing regimens, and the high risk of bias in one study. It is therefore unclear, based upon current published evidence, whether CCE-2 would be a suitable alternative test for patients who currently receive CT colonography.

The potential for delivering CCE-2 in the community for rural populations was explored in two small cohort studies, one in Israel and an unpublished study in Scotland. The possibility of delivering CCE-2 testing within the community is a potential advantage of CCE-2 over CT colonography and optical colonoscopy for rural populations that would otherwise have to travel significant distances to receive testing.

Studies exploring patient and public preferences relating to tests for colorectal polyps reported varying views.

Adverse events associated with the CCE-2 technology were reported in a small proportion of patients and consideration of individual patient characteristics may reduce the event rate further.

Cost-effectiveness of CCE-2 in patients with suspected colorectal polyps or cancer could not be ascertained as the only economic evaluation identified was based on a small primary study which found no statistically significant difference in sensitivity or specificity between CCE-2 and CT colonography.

## Identified research gaps

CCE-2 for detection of colorectal polyps appears to be at stage 3 'assessment via randomised controlled trials or alternatives' of the [IDEAL-D framework for medical devices](#).

Cost-effectiveness studies are needed that compare CCE-2 with optical colonoscopy or CT colonography from an NHS or UK societal perspective.

Qualitative studies exploring patient experiences of CCE-2, optical colonoscopy and CT colonography are desirable.

Planned and ongoing research in Scotland (appendix 3) could inform future decision-making on the use of CCE-2.



## 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.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on

[www.healthcareimprovementscotland.org](http://www.healthcareimprovementscotland.org)

## About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however 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 evidence note process see:

[www.healthcareimprovementscotland.org/our\\_work/clinical\\_cost\\_effectiveness/shtg/standard\\_operating\\_procedures.aspx](http://www.healthcareimprovementscotland.org/our_work/clinical_cost_effectiveness/shtg/standard_operating_procedures.aspx)

To propose a topic for an evidence note, email [shtg.hcis@nhs.net](mailto:shtg.hcis@nhs.net)

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network [www.knowledge.scot.nhs.uk](http://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](http://htaglossary.net).

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## Healthcare Improvement Scotland development team

- Jenny Harbour, Lead Author/Health Services Researcher
- Members of the SHTG evidence review committee

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## Appendix 1: 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<sup>29</sup>.

**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<sup>29</sup>.

**Positive likelihood ratio:** the probability that a positive test result will occur in a person with the target condition divided by the probability of a positive test result occurring in a person without the disease, that is the sensitivity divided by one minus specificity<sup>29</sup>.

**Negative likelihood ratio:** the probability that a negative test result will occur in a person with the target condition divided by the probability of a negative test result occurring in a person without the disease, that is the 1-sensitivity divided by specificity<sup>29</sup>.

**Positive predictive value:** the probability that a person with a positive test result is a true positive (has the disease)<sup>29</sup>.

**Negative predictive value:** the probability that a person with a negative test result is a true negative (does not have the disease)<sup>29</sup>.

**Receiver operating characteristic (ROC) curve:** a graph used to assess the ability of a diagnostic test to discriminate between people with or without the target condition. For most diagnostic test data the ROC curve plots sensitivity against 1-specificity for different cut-off values<sup>29</sup>. Area under the ROC curve (AUROC) can be used to compare the diagnostic accuracy of tests when multiple ROC curves are plotted on the same graph.



## Appendix 2: abbreviations

<b>CCE</b>	colon capsule endoscopy
<b>CI</b>	confidence interval
<b>CT</b>	computed-tomography
<b>FIT</b>	faecal immunochemical test
<b>FOBT/gFOBT</b>	faecal occult blood test/ guaiac faecal occult blood test
<b>LED</b>	light emitting diode
<b>MDS</b>	maximum differences scaling
<b>NPV</b>	negative predictive value
<b>NR</b>	not reported
<b>OR</b>	odds ratio
<b>PEG</b>	polyethylene glycol
<b>PPV</b>	positive predictive value
<b>SD</b>	standard deviation
<b>SE</b>	standard error

## Appendix 3: planned and ongoing work on CCE-2

In addition to the published studies identified in the main body of this evidence note, planned or ongoing research on CCE-2 in Scotland was sought. These projects are outlined in this appendix to provide an overview of unpublished Scottish research to inform decision-making in NHSScotland. A table of ongoing international trials is also presented to provide a global picture of ongoing research on this topic.

### *HICAP (NHS Highland)*

HICAP was a small feasibility study conducted in Skye and Ullapool 2016-17 to explore the use of CCE-2 in rural community settings. Forty patients presenting to their GP with symptoms of colorectal disease were offered CCE-2 at the local community centre instead of travelling to the nearest regional hospital for an optical colonoscopy. Images from the CCE-2 recording device were transmitted to Corporate Health International (Odense, Denmark) who provided the GP with an analysis of results within a few working days. The HICAP study is now being considered for wider roll-out through the ScotCap programme.

### *ScotCap (Scotland)*

ScotCap is a national group looking at Scotland-wide deployment of CCE-2 following the completion of the HICAP feasibility study. A ScotCap board has been set up comprising representatives from Scottish Government, the Digital Health & Care Institute, National Services Scotland and NHS boards. The ScotCap board will consider how best to deploy CCE-2 in Scotland and measure the impact of this intervention.

### *Economic analysis (University of Strathclyde)*

The Digital Health & Care Institute has funded an economic analysis at the University of Strathclyde which is due to report in autumn 2018. This economic analysis is a cost comparison of the current patient pathway versus a new patient pathway where FIT and CCE-2 results are used to determine referral to optical colonoscopy services. The data is based on the HICAP feasibility study and therefore takes into consideration patient travel to regional hospitals for optical colonoscopy. Benefits derived from the new pathway involving CCE-2 are expressed in economic terms as cost savings to the NHS. Preliminary results indicate direct costs of £1,092 per patient for optical colonoscopy and £899 for CCE-2. The incremental cost of the new pathway incorporating CCE-2 is estimated at £456 per patient and the total financial benefits accrued as approximately £620 per patient. In the sensitivity analysis these results are very sensitive to changes in the false negative rate (sensitivity) of CCE-2.

### *Market review (University of Strathclyde)*

The Digital Health & Care Institute has funded a second project at the University of Strathclyde to investigate CCE-2 devices currently available in the marketplace. The project is still in the early stages but aims to evaluate existing colon capsule devices against the needs of ScotCap stakeholders and to

conduct a non-systematic review of the literature describing different capsule devices. A more structured literature review focusing on stakeholder experiences of CCE-2 may also be produced. Proposed research questions for this review include ‘what factors predict uptake of CCE-2?’ and ‘what influences CCE-2 use in health services?’

#### *Clinical evaluation (Health Services Research Unit, NHSScotland)*

There are two strands to this project: a review being led by the University of Strathclyde (see project outline above) and a clinical evaluation being conducted within NHSScotland with support from the Health Services Research Unit (University of Aberdeen). The project is expected to run for 18 months starting from early July 2018 and will assess bowel preparation success rates, CCE-2 test completion rates, pathology found during CCE-2, the need for further diagnostic procedures and the pathology reported during these additional tests. The project aims to recruit 500 patients throughout NHS Highland, NHS Grampian, and NHS Western Isles.

#### *HICAP patient experiences (Glasgow School of Art)*

As a strategic partner, the Glasgow School of Art ran a workshop on behalf of the Digital Health & Care Institute to gather information about the experiences of people involved in the HICAP study. Patients contributed positive experiences, negative experiences, observations and direct quotes relating to the CCE-2 process.

The main positive experiences for CCE-2 related to being at home, where patients felt comfortable and did not have to worry about travel, time off work or dealing with unknown NHS staff. The main negative comment relating to CCE-2 was the need to go through the bowel cleansing process again and have an optical colonoscopy if a biopsy or other intervention were needed.

#### *Tayside referrals*

An undergraduate medical student project is exploring the proportion of patients referred to Ninewells hospital (Dundee) for optical colonoscopy who would be suitable for PillCam™ Colon 2.

### International ongoing studies

The table below outlines studies identified from international registers of ongoing trials that are investigating CCE-2 in patient populations of interest to this evidence note.

Trial ID	PICO	Country	Estimated completion date
<a href="#">NCT02826993</a> Can colon capsule endoscopy substitute CT colonography in the large bowel examination of persons whose colonoscopy was incomplete?	Patients: incomplete optical colonoscopy Intervention: CCE-2 (PillCam Colon 2™) followed by next-day CT colonography Outcomes: sensitivity and specificity measured in terms of number of polyps detected; polyp size estimation; polyp miss rate	Denmark	Aug 2018
<a href="#">UMIN000021936</a> Japan multicenter prospective study of usefulness, safety, and compliance of colon capsule endoscopy	Patients: established or suspected colorectal cancer Intervention: CCE-2 and optical colonoscopy Outcomes: completion rate; acceptability of CCE-2; bowel cleansing level; adverse events	Japan	Mar 2019
<a href="#">NCT03052335</a> The comparison of the efficiency of colon capsule endoscopy and optical colonoscopy in patients with positive immunochemical fecal occult blood test	Patients: positive FIT test Intervention: CCE-2 (PillCam Colon 2™) followed by optical colonoscopy Outcomes: NPV for polyps $\geq 10$ mm; accuracy for detection of advanced adenoma and colon cancer; patient acceptability; cost reduction from optical colonoscopies spared	Czech Republic	Dec 2019
<a href="#">NCT02738359</a> Efficacy of colonoscopy, colon capsule and fecal immunological test for colorectal cancer screening, in first degree relatives of patients with colorectal	Population: first-degree relatives of colorectal cancer patients Intervention: CCE-2, optical colonoscopy or FIT (randomised) Outcomes: colorectal neoplasia prevalence; rate of colorectal cancer;	France	Nov 2023

neoplasia: a prospective randomized study	complication rate; cost; quality of colon assessment		
<a href="#">UMIN000016636</a> Evaluation of the effectiveness of colon capsule endoscopy for FIT(FOBT) positive patients with no symptoms who are unsuccessful or difficult to perform colonoscopy	Patients: FIT/FOBT positive and unsuccessful or difficult optical colonoscopy Intervention: CCE-2 Outcomes: polyp detection rate; completion rate; examination time; cleansing state	Japan	NR
<a href="#">UMIN000012962</a> Prospective study for the diagnostic accuracy of colon capsule endoscopy	Patients: referred to optical colonoscopy for suspected colorectal disease Intervention: CCE-2 and optical colonoscopy Outcomes: diagnostic accuracy	Japan	NR
<a href="#">UMIN000012747</a> Open-label randomised comparative study of the detection rates of colorectal tumors/polyps between colon capsule endoscopy and CT colonography	Patients: positive FIT or symptoms of colorectal tumors/polyps Intervention: CCE-2 and CT colonography Outcomes: sensitivity and specificity; adverse events; examination time; compliance; detection rates	Japan	NR

NR = not reported