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Diagnostics Advisory Committee – Thursday 11 March 2024

PillCam COLON 2 for investigation of the colon through direct visualisation

The following documents are made available to the Committee:

1. **Final scope**
2. **Overview**
3. **Updated External Assessment Report produced by Sheffield Centre for Health and Related Research (SCHARR)**
4. **External Assessment Report consultation comments and responses**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

PillCam COLON 2 for investigation of the colon through direct visualisation

Final scope

August 2024

1 Introduction

The topic selection oversight panel identified PillCam COLON 2 as suitable for evaluation by the Diagnostics Assessment Programme based on a topic briefing. The final scope was informed by discussions at the scoping workshop on 3 August 2023 and the assessment subgroup meeting on 17 August 2023. A glossary of terms is provided in appendix A.

2 Description of the technology

This section describes the properties of the diagnostic technology based on information provided to NICE by manufacturers and experts, and on information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

Colorectal polyps are small growths on the inner lining of the colon. Polyps are not usually cancerous. However, some may develop into adenomas (adenomatous polyps) which can be precancerous. People with adenomas have a higher risk of developing colorectal cancer if the adenomas are not removed. People with suspected colon cancer are referred for a colonoscopy to look for bowel cancer and polyps. Optical colonoscopy is an invasive procedure done at the hospital. If during a colonoscopy, abnormal tissues or polyps are identified, a biopsy can be taken, or polyps can be removed as part of the procedure (polypectomy).

NHS endoscopy services are under considerable strain and there are long waiting lists for colonoscopy. These capacity constraints have worsened since the Covid-19 pandemic. Clinicians have observed that many people on the suspected colorectal cancer referral pathway have no abnormal pathology found at colonoscopy. Colon capsule endoscopy (CCE) is a non-invasive method that involves a small capsule with 2 embedded cameras being swallowed, allowing the colon to be visualised. This could be used as an alternative to colonoscopy to help rule out polyps and colon cancer. CCE, may thus be used as a filter or triage test, so that therapeutic colonoscopy can be used for people who need a biopsy or polypectomy. This may help reduce endoscopy service waiting lists and aid early cancer detection by prioritising people who need further tests and treatment.

2.2 Product properties

2.2.1 PillCam COLON 2

PillCam COLON 2 (Medtronic) is a type of CCE technology which provides visualisation of the colon for detecting polyps and other abnormal bowel pathology. The system consists of 3 components: the capsule, recorder with sensors, and desktop software. The single use capsule contains 2 cameras, light emitting diodes to illuminate the area around the cameras, a battery, and antenna. The capsule is swallowed under clinical supervision following a bowel cleansing routine starting the day before. For both CCE and colonoscopy laxatives are provided. However, for CCE, in addition to the preparation, 'booster' laxatives are taken after the capsule has been swallowed to promote continued movement of the capsule through the colon until it comes out. The capsule captures images at either 4 or 35 frames per second over the course of 10 or more hours, depending on how fast it moves through the colon. The patient wears a sensor belt or sensor leads which are attached to a data recorder. Images are sent from the capsule to the data recorder using radiofrequency. After the capsule is excreted, the raw data is processed using PillCam desktop software and compiled into a video for review. Once the COLON 2 capsule study is downloaded, it can be uploaded to the Pillcam Cloud Reader software. This provides a secure platform to review the study remotely and can then be sent back to the original study or network location. The user can play, rewind and fast-forward the video whilst marking anatomical landmarks and thumbnails

containing images of interest. After viewing the video and creating the findings, an interpretation of the study can be summarised in a patient report. The video and report must be interpreted by skilled personnel.

PillCam COLON, which was launched in 2006, is the previous version of PillCam COLON 2 (launched in 2010). Adaptations were made following initial studies and incorporated into the PillCam COLON 2. Changes include:

- moving from a fixed frame rate where a fixed number of images were taken to an adaptive frame rate where the number of images taken depends on the speed of travel (varies from 4 to 35 images per second).
- increased field of view from 156º to 172º, providing a near 360º view
- updated D3 recorder to take images for 10-12 hours

The company states that the sensitivity in detecting polyps larger than 6mm and smaller than 10mm increased substantially between PillCam COLON and PillCam COLON 2.

Other PillCam capsules are available such as PillCam SB 3 capsule or PillCam Crohn's capsule. However, this assessment focuses on PillCam COLON 2 only as this is the only product to visualise the colon to detect polyps or colon cancer.

3 Target conditions

3.1 Colorectal polyps and colorectal cancer

Bowel polyps are very common, affecting about 15-20% of the UK population aged 50 or over.

Polyps can be described in terms of their shape, size and location. The shape of a polyp can be defined according to the Paris endoscopic classification:

- Type 0-Ip: protruded, pedunculated (on a stalk)
- Type 0-Is: protruded, sessile (flat against the surface, slightly raised)
- Type 0-IIa: superficial, elevated
- Type 0-IIb: flat
- Type 0-IIc: superficial shallow, depressed

- Type 0-III: excavated (depressed)

Based on the British Society of Gastroenterology (BSG) / Association of Coloproctology of Great Britain and Ireland (ACPGBI) and European Society of Gastrointestinal Endoscopy (ESGE) guidelines risk stratification is based on the size and number of polyps:

- High risk patients: 2 or more pre-malignant polyps including at least 1 advanced polyp (serrated polyp or an adenoma measuring at least 10mm in size or containing dysplasia [if a polyp looks like cancer under a microscope]), or 5 or more pre-malignant polyps (serrated or adenomatous) of any size
- Intermediate risk patients: 1 polyp measuring 6 to 9mm or 3 to 4 polyps of any size
- Low risk patients: less than 3 polyps all measuring less than 6mm that are not considered clinically significant.

Risk factors for colorectal polyps include older age, genetics and family history of bowel polyps or bowel cancer, dietary and lifestyle factors and conditions that affect the gut such as colitis or Crohn's disease.

Most bowel polyps do not cause any symptoms, so most people are unaware that they have them. However, some larger polyps can cause:

- Rectal bleeding
- Mucus in stool
- Diarrhoea or constipation
- Abdominal pain

Most are not cancerous but some types of polyps such as adenomas may develop into colorectal cancer if undiagnosed and untreated. Experts believe that most bowel cancers develop from adenoma polyps. Colorectal cancer is the fourth most common cancer in the UK with approximately 43,000 new cases and around 16,800 deaths per year (Cancer Research UK). Almost half of the people diagnosed with colorectal cancer in England and Wales survive at least 10 years after diagnosis. Early diagnosis is thought to improve survival.

Colorectal polyps are usually picked up during screening for bowel cancer or when the bowel is investigated for another reason.

3.2 Diagnostic and care pathway

3.2.1 Referral on suspected cancer pathway

A suspected cancer pathway referral means an urgent referral directly by the GP after a clinical assessment of symptoms. The referral would be for the most appropriate test (for example, colonoscopy or CT colonography), or an urgent appointment with a specialist.

Faecal immunochemical testing (FIT) is designed to detect small amounts of blood in a faecal sample by using antibodies specific to human haemoglobin. A positive FIT alone cannot confirm a diagnosis of colorectal cancer. It is the primary test used in the NHS bowel cancer screening programme for 2-yearly testing of asymptomatic people aged 60 to 74. FIT was recently recommended by NICE to guide referral in primary care for people with symptoms that may be indicative of colorectal cancer (DG56). It recommends using a FIT threshold of 10 micrograms per gram of faeces. NICE's guideline NG12 on suspected cancer: recognition and referral includes a description of the clinical signs and symptoms indicative of colorectal cancer where the FIT test is recommended to be used. This aligns with guidance on FIT from the Association of Coloproctology of Great Britain & Ireland (ACPGBI) and the BSG published in 2022 which recommended FIT be used for all people with clinical features of colorectal cancer to prioritise referral for urgent investigation. Many centres have already adopted this approach.

3.2.2 Post-polypectomy surveillance

Following findings on a previous colonoscopy people may be scheduled for a follow up surveillance colonoscopy or colorectal imaging. The BSG guidance on post-polypectomy and post colorectal cancer resection surveillance recommends that people who are at high risk for future colorectal cancer following polypectomy should undergo a one-off surveillance colonoscopy at 3 years. The high-risk criteria for future CRC following polypectomy include either:

- Two or more premalignant polyps including at least 1 advanced colorectal polyp which is defined as a serrated polyp (a slightly raised area or bulge) of at least 10mm in size or containing any grade of dysplasia (if a polyp looks like cancer under a microscope), or an adenoma of at least 10mm in size or containing high-grade dysplasia, or
- 5 or more premalignant polyps.

3.2.3 Existing guidance on where CCE may be used

3.2.3.1 Screening population

The European society for medical oncology (ESMO) clinical practice guidelines for localised colon cancer (2020) states that capsule colonoscopy is not recommended for screening.

The European society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) released updated guidance on imaging alternatives to colonoscopy in 2020 which also suggests that CCE should not be used as a first line screening test for colorectal cancer. However, they do suggest that use of CCE could be considered (where available) in the case of incomplete or unfeasible colonoscopy within organised population screening programmes.

3.2.3.2 Symptomatic population

The Colon capsule endoscopy: ESGE Guideline published in 2012 states that CCE is feasible and safe, and appears to be accurate when used in people with average risk of developing colorectal cancer.

In August 2020 the Scottish Health Technologies Group (SHTG) assessed the clinical and cost effectiveness of PillCam COLON 2 compared with optical colonoscopy or CT colonography for identifying colorectal polyps in adults with signs or symptoms of colorectal cancer or at increased risk of colorectal cancer. SHTG recommended that CCE 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 an abnormal FIT test. The clinical effectiveness evidence and economic analysis

indicated that CCE should be reserved for people at lower risk of colorectal cancer. Since then, new evidence has been published and an Innovative Medical Technology overview has been produced for consideration alongside the 2020 SHTG recommendations.

In November 2020 a clinical guide for triaging patients with lower gastrointestinal symptoms (2020) was released on how to prioritise and triage patients referred onto a 2 week wait pathway during the coronavirus pandemic which included the use of colon capsule endoscopy for prioritised endoscopy or colonic imaging for people with:

- NG12 specified symptoms, with a FIT 10-100 micrograms of haemoglobin per gram of faeces.
- Other NG12 specified symptoms with a FIT >100 micrograms of haemoglobin per gram of faeces who have had a colonoscopy requiring no further investigation in the previous 3 years.

The guide states that the use of colonic imaging depends on local capacity, clinical prioritisation, and patient factors. It also states that where colon capsule is used, robust data collection and follow up procedures must be in place.

The BSG (2022) conducted a review on colon capsule endoscopy and also suggested that CCE may be best suited for use in low-risk patients with a FIT of <10 micrograms of haemoglobin per gram of faeces, because a subsequent colonoscopy is less likely to be needed in this population.

3.2.3.3 Surveillance population

The company provided a clinical guide for using colon capsule endoscopy in post-polypectomy surveillance patients for the NHS England CCE pilot study which states that those awaiting surveillance are at low risk of cancer or have a small risk of significant premalignant polyps. These patients may be appropriate for and benefit from CCE because they are less likely to need a therapeutic colonoscopy.

The ESGE/ESGAR 2020 guideline update states that there is insufficient evidence to recommend CCE in post-polypectomy surveillance.

3.2.3.4 Following incomplete colonoscopy

The ESGE/ESGAR 2020 guideline update recommends that use of CCE can be considered where available preferably the same or next day following an incomplete colonoscopy.

3.2.3.5 When colonoscopy is contraindicated or not possible

The ESGE/ESGAR 2020 guideline update does not recommend CCE for people with alarm symptoms where colonoscopy is contraindicated or not possible because of a lack of evidence. However, it suggests that it may be considered in patients with non-alarm symptoms where available.

3.2.4 Existing guidance on CCE follow up

The Colon capsule endoscopy: ESGE 2012 Guideline recommends that patients found to have a polyp measuring 6mm or more at CCE, as well as those with 3 or more polyps (of any size), should be sent for post-CCE colonoscopy for polypectomy.

A clinical guide for using CCE in the lower gastrointestinal pathway was published following funding allocated by the National Cancer Team to pilot CCE clinics to support restoration of endoscopy services during the COVID-19 pandemic. This recommends, based on the European guideline, that patients should be referred for colonoscopy in line with the following:

- Patients found to have a polyp measuring 6mm or more and those with 3 or more polyps, irrespective of size, should be sent for post-CCE colonoscopy for polypectomy.
- If polyps found on the reading are deemed to be hyperplastic (non-cancerous), teams should use their clinical judgment to decide if a referral to colonoscopy is appropriate.

A clinical guide for using colon capsule endoscopy in post-polypectomy surveillance patients in the NHS England CCE pilot study recommends that patients should be referred to colonoscopy in accordance with the following:

- **Tier 1**: high-risk premalignant polyps identified (1 polyp measuring 10mm or more or 5 or more polyps of any size based on BSG/ACPGBI guidance): proceed directly to therapeutic colonoscopy,
- **Tier 2**: intermediate-risk polyps identified (1 polyp measuring 6 to 9mm or 3 to 4 polyps of any size on ESGE guidance): deferred therapeutic colonoscopy within 1 year,
- **Tier 3**: low-risk polyps identified (less than 3 polyps all measuring less than 6mm based on ESGE guidance): surveillance colonoscopy at 3 years,
- **Tier 4**: no polyps identified: discharge with safety netting in place.

Clinical experts noted that people with high-risk polyps identified using CCE would be referred onto the 2-week wait pathway for a therapeutic colonoscopy and that those with intermediate risk polyps would likely be referred on a routine pathway.

The ESGE/ESGAR 2020 guideline update suggests that follow up CTC may be clinically considered for polyps identified via CCE that measure between 6mm and 9mm if patients do not undergo polypectomy because of patient choice, comorbidity and/or low risk profile for advanced neoplasia.

3.2.5 Diagnosis of colorectal polyps and cancer

Colonoscopy is often used for diagnosing colorectal cancer in people without major comorbidities. It can visualise the entire colon and biopsies can be taken and examined histologically to confirm a diagnosis, unless this is contraindicated (for example, in people who have recently had a heart attack). Polyps can also be removed as they are identified. However, clinical experts advised that this is dependent on the skill level of the person performing the colonoscopy and that some colonoscopies will only be diagnostic rather than therapeutic. It is most frequently performed as an outpatient procedure. It requires adequate preparation of the colon using diet modification and laxatives. It is estimated that in around 5% to 20% of people referred for colonoscopy, the procedure cannot be completed. This can be due to people not following the bowel cleansing process correctly, unusual anatomy which may obstruct the colonoscope, or patient intolerance of the procedure. Most people undergoing the procedure are offered sedation, painkillers, or nitrous oxide gas. It is associated with very rare but serious complications, such as perforation of

the bowel and heavy bleeding that may require a transfusion. Clinical experts noted that colonoscopy is not a perfect test and can miss important signs of disease.

Because of its invasive nature and the risk of dehydration during colon preparation, colonoscopy may not be suitable for elderly people and those with comorbidities such as kidney disease. For those people CT colonography, which is less invasive than conventional colonoscopy, is an alternative imaging investigation of choice. CTC is also an option for people with an incomplete optical colonoscopy. It involves using a CT scanner to produce 2- and 3-dimensional images of the entire colon and rectum. People having a CTC need to consume a contrast-based material, require air insufflation and are exposed to potentially harmful ionising radiation. Both optical colonoscopy and CTC require patients to undergo a period of bowel cleansing, although it is less intensive for CTC. ACPGBI/BSG guidance recommends that CT colonography is equivalent to colonoscopy for detection of colorectal cancer, and the choice should be determined by local expertise and availability.

Clinical experts advised that, for some people, other diagnostic techniques such as flexible sigmoidoscopy may be appropriate to investigate lower gastrointestinal symptoms. Experts in secondary care said that, where available, FIT results are often used to inform the choice of further investigation based on capacity (see section 6.3).

3.2.6 Treatment of colorectal polyps and cancer

The most common finding during a colonoscopy is colorectal polyps, which can be removed using cauterisation or a snare. In rare cases, surgery may be needed to treat polyps by removing part of the bowel. This is only done if the polyp is very large, has cell changes, or there are a lot of polyps. Clinical experts advised that polyp removal cannot always be undertaken in the initial colonoscopy depending on the skill level of the person performing it and that sometimes a follow up therapeutic colonoscopy will need to be scheduled. After bowel polyps are removed, they are sent for testing in a laboratory. Some types of polyps (called adenomas) can become cancerous. If colorectal cancer is confirmed, NICE's guideline on colorectal cancer recommends further imaging tests, such as CT or MRI, to stage the cancer and determine what treatment is needed. Colonoscopy may also find other bowel diseases such as Crohn's disease, ulcerative colitis and diverticulosis, which may

need further treatment and follow-up. People with no abnormalities detected during colonoscopy may be referred for further testing if a clinician thinks this is needed.

3.3 Patient issues and preferences

The Scottish Health Technologies Group (SHTG) assessed the clinical and cost effectiveness of PillCam COLON 2. During the evaluation, they received a patient organisation submission from Bowel Cancer UK outlining specific patient considerations regarding CCE and colonoscopy. New evidence has become available since the SHTG recommendations (2020), and an Innovative Medical Technical Overview on CCE for the detection of colorectal polyps and cancer was published (SHTG, 2024). It reported patient views on user experiences and acceptability. The British Society of Gastroenterology conducted a review on colon capsule which also reported on patient experience.

NHS endoscopy services are under considerable strain and there are long waiting lists for colonoscopy. Waiting for medical tests can induce anxiety, especially if there is a potential risk of cancer. Having the option of accessing colon capsule endoscopy earlier than colonoscopy can potentially reduce some of the 'waiting anxiety'. However, clear communication to the person is needed around why colon capsule is offered, what is expected during the procedure and the potential benefits. Test results are not immediately available and further tests including a therapeutic colonoscopy or flexible sigmoidoscopy may be needed depending on the results. Some people may prefer to wait for a colonoscopy. Lay experts emphasised that options should be discussed between the patient and clinician as part of shared decision making. Clinical experts also noted that pre-assessment is important to check for suitability for colon capsule.

Before swallowing the colon capsule, bowel preparation is needed to clear out the bowel. This includes a low fibre diet for about 5 days before the test, no food consumption on the day of the test and taking laxatives at different time points to empty the bowel. Taking laxatives means that people need to be near a toilet, and the process can be very unpleasant. Up until this point, the bowel preparation process is the same for colonoscopy and CCE. However, after swallowing the capsule, further 'booster' laxatives are given to promote colonic motility and capsule

excretion. Lay experts mentioned the need for having clear communication in explaining the bowel preparation process to the person undergoing the procedure. It is up to the clinicians to determine which bowel preparation regimen and diagnostic test is suitable, and experts emphasised that age, weight, comorbidities and level of frailty should be taken into account. Lay experts also noted that people with reduced dexterity or other disabilities such as visual impairment may need extra support to swallow the capsule and set up the sensor belt or leads.

CCE appears to be more comfortable, acceptable to and preferred by patients (SHTG, 2024). Compared with colonoscopy, it can be done at home, and is associated with reduced procedure-related distress such as anxiety, discomfort and embarrassment (Parisi, 2024; Ismail, 2022). It also does not need sedation. During a colonoscopy some air is pumped into the colon which may cause bloating or a feeling of cramping in the abdomen. Some people find having a colonoscopy uncomfortable, but most people do not report that it is painful. People having colonoscopy may also be concerned about the adverse effects of the colonoscopy, such as heavy bleeding or perforation of the bowel. Some people may also be hesitant towards undergoing CT colonography because it involves ionising radiation. Clinical experts noted that this is particularly a concern among people aged 30 or younger.

4 Comparator

The comparators are colonoscopy and CT colonography.

5 Scope of the assessment

Table 1: Scope of the assessment

Decision question	Does the use of colon capsule endoscopy in adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer or those due to have post-polypectomy surveillance 3 years after their index colonoscopy represent a clinically and cost-effective use of NHS resources, taking into consideration potential colonoscopy capacity constraints?
Populations	1. Adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer who are referred to secondary care.

	Where evidence is available, subgroups for this population may include: ○ People with a FIT score between 10-100 micrograms of haemoglobin per gram of faeces ○ People with a negative FIT result of <10 micrograms of haemoglobin per gram of faeces with concerning clinical symptoms Clinical experts advised that the technology is not appropriate for use in people with rectal or anal mass or anal ulceration and that this group should be excluded from the scope. 2. Adults who are due to have a post-polypectomy surveillance colonoscopy at 3-years because of high-risk findings at their index colonoscopy Where evidence is available, subgroups may include: • People who have declined optical colonoscopy • People who have had an incomplete optical colonoscopy despite adequate bowel preparation
Intervention	PillCam COLON 2
Comparators	• Colonoscopy • CT Colonography
Reference standard	The reference standard for examining the colon and assessing the accuracy of CCE is optical colonoscopy. Other reference standards will be considered where data using the preferred reference standard is unavailable.
Healthcare setting	Secondary care. The intervention may be delivered in primary care or the community
Outcomes: intermediate measures	Intermediate measures for consideration may include: • Diagnostic accuracy for detecting polyps (per patient and per lesion) ○ Measuring less than 6mm ○ Measuring between 6 and 9mm ○ Measuring 10mm or more • Diagnostic accuracy for detecting: ○ Colorectal cancer ○ Other bowel pathology including IBD • Capsule completion rates (including excretion of the capsule within its battery life with complete visualisation of the colon) • Bowel cleansing level (adequate vs. inadequate) • Detection rates with CCE, colonoscopy or CTC for: polyps (including adenomas); cancer; other bowel pathology

	• Uptake • Reduction in number of colonoscopies/number of colonoscopies potentially prevented (diagnostic, therapeutic, urgent and non-urgent) • Proportion of people requiring follow up colonoscopy or other investigations such as flexible sigmoidoscopy after CCE/colonoscopy and CTC (diagnostic, therapeutic, urgent, non-urgent) • Number of polyps missed (including high-risk, intermediate risk and low risk polyps) • Numbers of cancers missed
Outcomes: clinical	Clinical outcomes for consideration may include: • Number of colorectal cancer diagnoses • Stage of detected cancers • Number/proportion of people identified with other bowel pathologies • Number/proportion of people with advanced adenomas detected or detected and treated • Morbidity including adverse events associated with CCE, colonoscopy and CT colonography • Mortality
Outcomes: patient-reported	Patient-reported outcomes for consideration may include: • Health related quality of life • Anxiety associated with waiting for procedures or test results because of diagnostic delays, and further diagnostic workup • Preference for CCE versus colonoscopy or CT colonography
Outcomes: costs	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of device (including consumables, software, maintenance, service costs and patency capsule) • Cost of staff (including pre-assessments, supervision of swallowing, reading and reporting time) and associated training • Costs of follow up testing and care including colonoscopy • Costs associated with CCE and other investigations • Implementation costs • Costs of treating cancer • Medical costs of adverse events from the procedure or further diagnostic work up, including those associated with false test results and inappropriate investigations
Measuring cost-effectiveness	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.

Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

6.1 Existing models

The SHTG conducted a cost comparison analysis which compared the current colon diagnostic pathway with a new pathway that includes CCE. The analysis was updated using ScotCap data from 2023, including new prices (SHTG, 2024). A full economic evaluation of the impact of CCE was not carried out and equal diagnostic accuracy between CCE and optical colonoscopy was assumed. The population consisted of two groups, symptomatic and surveillance patients. The models were built around the assumption that a proportion of people receiving CCE receive a negative result and do not need further testing including colonoscopy, while a proportion undergoing CCE would subsequently be referred for additional examination because of incomplete CCE or positive findings.

6.2 Ongoing NHS England pilot study

In March 2021, NHS England announced that some people with symptoms of bowel cancer may have colon capsule endoscopy instead of having a colonoscopy straight away. NHS England is conducting a pilot study which aims to evaluate the diagnostic accuracy of CCE in the following populations 1) adults referred with suspected colorectal cancer through the 'two week wait' pathway who have a FIT result between 10-100 micrograms of haemoglobin per gram of faeces, or adults with a negative FIT result (<10 micrograms of haemoglobin per gram of faeces) who have been referred onto the urgent cancer pathway because of concerning symptoms, 2) adults who are due to have a post-polypectomy bowel surveillance colonoscopy 3 years after the index colonoscopy. The pilot study aimed to include 11,000 people and recruitment to the study closed at the end of March 2024., Results are expected in the summer or autumn in 2024.

6.3 Colonoscopy and CT colonography capacity for urgent referrals and surveillance

There are currently long waiting lists for colonoscopy. A letter published by NHS England states that, since the pandemic, waits on the lower gastrointestinal pathway have lengthened more than for any other tumour group. In June 2023, 15% of people seen by a specialist for suspected lower gastrointestinal cancer were not seen within 2 weeks of urgent referral, and 43% did not have a diagnosis within 28 days (NHS cancer waiting times, June 2023)

During scoping of the diagnostics assessment on quantitative FIT, stakeholders highlighted that colonoscopy capacity is limited and therefore the Diagnostics Advisory Committee will need to consider real-world constraints during the decision-making process.

There are ongoing pressures on endoscopy services with backlogs in the symptomatic population. It has been estimated that 15% of the colonoscopies performed in the UK each year are for polyp surveillance (Rutter et al. 2019). It has been suggested that CCE can potentially play a big role in reducing the backlogs, specifically for the surveillance population. People at low risk of colorectal cancer on the waiting list for a surveillance colonoscopy can be diverted to CCE. The NHS England CCE pilot has been extended to people who are due or overdue for a post-polypectomy surveillance colonoscopy in the symptomatic endoscopy service. This is to support prioritisation of colonoscopy capacity for those at the highest risk of colorectal cancer.

Clinical experts have advised that depending on how it is implemented CCE could potentially release capacity to endoscopy services. Clinical experts noted that the main potential benefit of CCE could be colonoscopy reduction but that patient selection is likely to be important. In current practice, there are lists for diagnostic and therapeutic colonoscopies. Bowel pathology is a key indicator in determining which list people need to be on. Without knowing the bowel pathology, people may end up on the diagnostic list and if abnormal bowel pathology is found they need to be referred for a therapeutic colonoscopy. This is because not everyone who does colonoscopies is trained to remove polyps and polyp size also plays a factor. CCE

could potentially be used to identify polyps and ensure that people end up on the right list, depending on what is found. Experts also noted that the increase in endoscopy capacity could potentially be used to lower the NHS bowel cancer screening programme threshold.

Experts noted that CCE could potentially allow for more efficient use of staff by having nurse endoscopists reading the capsules. In some trusts nurse endoscopists do the reading, reporting and sign off, while other trusts have implemented double reading strategies where a nurse endoscopist does the initial reading and reporting and this can be signed off by a consultant. Reading of CCE recordings could also be outsourced or done in centralised reading hubs. This can be done by using the Pillcam Cloud Reader software, which is a secure platform where COLON 2 capsule studies can be uploaded and reviewed remotely.

The assessment should consider the constraints of current colonoscopy capacity and the impact of this on outcomes specified in the scope, including waiting times for colonoscopy services. It should also consider the potential impact of CCE on capacity for endoscopy services.

6.4 CCE in primary care and community settings

CCE can be done in primary care and community settings under the supervision of secondary care. The benefits of doing CCE in these settings include that people do not need to travel during intensive bowel preparation and it can reach people who live remotely increasing accessibility and inclusivity. Clinical experts advised that CCE could potentially be used in the following 3 settings: 1) in primary care (e.g., GP surgery) or community diagnostic centres, 2) at home under guidance of community nurse or health visitor, and 3) at home where the colon capsule, medications for bowel preparation, and guidance are posted to the person to conduct the test alone. After completing the test at home the belt and recorder are returned to secondary care the next day. The company noted that in some cases the equipment (data recorder and sensor belt or sensor leads) can be returned using a courier service. However, clinical experts noted the risk of aspiration of the capsule and said that even though it is possible to do CCE in these settings, currently CCE is mostly done in secondary care. They emphasised that swallowing should be

supervised by clinical staff regardless of the setting. A recent study (Parisi, 2024) trialled using a video call to supervise the swallowing of the capsule.

6.5 Safety netting and other conditions with gastrointestinal symptoms

The proposed approach of using CCE to detect colon polyps could result in people with a negative CCE or benign disease, being discharged from secondary care and not being referred for further investigation with colonoscopy or CT colonography. However, these investigations can also be used to diagnose other conditions such as Crohn's disease, ulcerative colitis and diverticulosis, which may need further treatment and follow up. If CCE is not as good as colonoscopy in picking up these conditions, then use of CCE may introduce a delay to diagnosis for people with these conditions.

Safety netting refers to processes used to avoid missing disease (cancer or otherwise) in people with negative test results.

The clinical guide for using CCE in the lower gastrointestinal pathway states that following a negative CCE or a benign disease identification most people will return to primary care. This decision needs to be clearly communicated to the patient and GP. Patients need a formal review at 6 weeks to ensure that their symptoms have resolved or are adequately treated. If they are still symptomatic after 6 weeks, then they need to be re-referred to secondary care.

6.6 Bowel preparation

The ESGE guideline on colon capsule endoscopy states that the quality of the bowel preparation is associated with the accuracy of the CCE procedure. Bowel preparation is extremely important to ensure a CCE test is successful as it will affect the ability of the capsule to visualise the whole colon. Faeces, cloudy fluids, or bubbles may hinder mucosal visualisation by CCE. The capsule is unable to blow air into the colon, remove fluids, wash the mucosal surface, or move actively through the colon. Therefore, the cleansing protocol for CCE aims to 1) adequately cleanse the colonic mucosa, 2) fill the colon with clear fluids to improve visualisation and decrease the number of air bubbles, and 3) facilitate the movement of the capsule

through the colon before the battery runs out. Bowel preparation may impact on the accuracy of CCE and therefore may need to be considered as part of this assessment.

6.7 Use of patency capsule

A patency capsule may need to be used in cases where there is risk of retaining the capsule within the small bowel. The risk of this occurring is very low in the general population, but higher in people with Crohn's disease. If a CCE capsule is retained the person may require endoscopic retrieval or a surgical intervention, depending on the location of retention.

Clinical experts advised that patients should be assessed for risk of retention as part of a pre-assessment for suitability for CCE. If there is suspicion of blockage or narrowing in the small bowel, a patency 'dummy' capsule can be given before CCE. The capsule is the same size as CCE and is designed to dissolve after 30 hours.

6.8 Reading times and reporting for CCE

Clinical experts said that reading times and reporting of CCE results can take between 45 to 60 minutes, depending on the speed they are viewed at, and how long it took for the capsule to be excreted. A review done by the BSG on colon capsule endoscopy reported that the imaging from each of the 2 cameras is viewed separately. If viewed at 12 frames per second, it would take about 50 to 60 minutes. It can be viewed at a quicker speed, but this may risk missing small polyps. It also states that the use of artificial intelligence (AI) is likely to change this practice. Clinical experts said that there is no AI for reading the capsules to date but are aware that colonic algorithms are in development and studies are ongoing.

6.9 Environmental sustainability in endoscopy

The BSG, Joint Accreditation Group (JAG) and Centre for Sustainable Health (CSH) (2022) published a joint consensus on practical measures for environmental sustainability in endoscopy. It states that gastrointestinal endoscopy is highly resource intensive and contributes significantly to greenhouse gas emissions and waste generation. It recommends that sustainable conventional diagnostic endoscopy, such as CT colonography and CCE for bowel cancer screening, should

be considered in all patients where it is clinically indicated. Clinical experts also advised that CCE can potentially have a positive environmental impact by reducing patient travel if CCE is done in a community setting as well as the carbon footprint that is associated with traditional colonoscopy (including the chlorine used to clean scopes and the use of plastic). The clinical experts noted that these benefits are not always considered but the NHS England pilot study may be collecting some data related to environmental sustainability and thus may need to be considered in the evaluation.

6.10 NIHR funding call

The National Institute for Health and Care Research (NIHR) has put out a funding call '22/168 The diagnostic accuracy of colon capsule endoscopy commissioning brief'. Stage 2 applications will be discussed at the funding committee in September 2023. It will address the following research question: what is the diagnostic accuracy of colon capsule endoscopy compared to standard colonoscopy? The research call encourages applicants to consider multiple patient groups requiring colonoscopy because small studies indicate that CCE may be of use in a wider population. Asymptomatic people referred via the colon cancer screening programme are excluded from the proposed study. The study is proposed to inform future practice, guidelines, and patient choice.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

PillCam COLON 2 should not be used for people with known or suspected gastrointestinal obstruction, strictures or fistulas. It should also not be used for people with swallowing disorders, and it is contraindicated for people with cardiac pacemakers or other implanted electromedical devices. However, clinical experts noted that there are studies that show that the capsule does not interfere with the pacemaker, and it is safe for use. In addition, it may not be suitable for people who are pregnant, people with Crohn's disease, people with long term daily use of non-

steroidal anti-inflammatory drugs, people with small bowel resection, people with abdominopelvic irradiation or people who are frail.

Colorectal polyps are more likely in older people, people with conditions that affect the gut such as colitis or Crohn's disease, people with a family history of colorectal polyps or colon cancer, people from Black African or Caribbean family backgrounds, Jewish people of central and eastern European family origin, people who are overweight or people who smoke. Colorectal polyps may be slightly more prevalent in men. People with cancer are protected under the Equality Act 2010 from the point of diagnosis. Age, sex, race, pregnancy and maternity, and disability are protected characteristics under the Equality Act (2010).

People with a learning disability have a lower completion rate for CCE and also have a higher rate of death from colon cancer compared with the general population. People who are less mobile, for example due to physical disability or frailty, have lower completion rates for CCE than those who are more mobile. Completion rates may also be higher in men.

Colorectal cancer disproportionately affects people from low socioeconomic backgrounds. They may have difficulties accessing health services because they may not or cannot go to hospital. Having the option of doing CCE in a primary or community care setting, with supervision from a healthcare professional, may allow for greater accessibility and inclusivity for people from lower socioeconomic backgrounds.

People who do not speak or understand English or people from ethnic minority family backgrounds may be harder to reach and have lower uptakes of diagnostic screening tests for bowel cancer. Lay experts mentioned that sometimes it falls on family members to come to appointments and translate, which may not always be possible.

Invasive procedures, such as colonoscopy, may be less acceptable in some cultures. Furthermore, it may be unsuitable for people who are on anti-coagulants that should not be stopped for a diagnostic procedure.

8 Potential implementation issues

Potential barriers and enablers to implementation include:

Care pathway

- Clinical experts noted that most of the diagnostic pathways are overseen by surgical departments, including the 2 week-wait referral pathway. They emphasised that education and training of CCE is key and would also be needed to create awareness of this diagnostic option. Colonoscopy is the gold standard and may still preferred by clinicians.
- The endoscopy services currently sit within secondary care. CCE can be done in primary care and community settings (see section 6.4). However, clinical experts raised some concern about CCE being done in primary care or the community, specifically with regards to the reading and reporting of CCE. If CCE is delivered in a community setting with capsules being sent to people's homes, experts advised this needs to be done under the control of secondary care. There are established processes for colonoscopy and CT colonography and having it all within secondary care helps with tracking people and triaging them appropriately. If people need a therapeutic colonoscopy following CCE this can be arranged within the same centre.

Colonoscopy capacity and waiting times

- There are large variations in wait times among NHS Trusts. Implementation of CCE has the potential to reduce the number of colonoscopies needed, allowing those most in need to be seen more quickly.
- Clinical experts advised that using nurse endoscopists instead of consultants for reading capsules and triaging patients can potentially help with the uptake of CCE and increase endoscopy capacity. However, it should be noted that resources are required to train nurses in reading CCE recordings and that time is needed to download the video, read and report the findings.

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Appendix A Glossary of terms

Adenoma

A tumour or growth that is not cancerous (benign).

Advanced adenomatous polyp (synonymous with advanced adenoma)

An adenoma of at least 10mm in size or containing high-grade dysplasia.

Advanced colorectal polyp

Includes both advanced serrated polyps and advanced adenomatous polyps.

Advanced serrated polyp

A serrated polyp of at least 10mm in size or containing any grade of dysplasia.

Colonoscopy

An investigation that allows doctors to examine the lining of the colon (large intestine) using a flexible tube that contains a camera and light source (colonoscope).

Colon capsule endoscopy (CCE)

An investigation in which a person swallows a small capsule containing cameras. This takes pictures of the lining of the colon and communicates them wirelessly to a nearby receiver.

Computed tomography colonography (CTC)

A test that uses CT scans to check the colon and rectum.

Faecal immunochemical test (FIT)

A test which detects faecal occult blood using antibodies against human haemoglobin.

Flexible sigmoidoscopy

An investigation that allows doctors to examine the lining of the lower section of the colon (sigmoid) using a flexible tube that contains a camera and light source (sigmoidoscope).

Polyp

A small growth on the inner lining of the colon or rectum.

Polypectomy

Removal of polyps

Premalignant polyp

The term includes both serrated polyps (excluding small (1–5mm) rectal hyperplastic polyps) and adenomatous polyps. It does not include other polyps such as post-inflammatory polyps.

Serrated polyp

The umbrella term used to describe hyperplastic polyps, sessile serrated lesions, SSLs with dysplasia, traditional serrated adenomas, and mixed polyps.

Diagnostics Guidance

PillCam COLON 2 for investigation of the colon through direct visualisation

Assessment report overview

This overview summarises key information from the assessment and sets out points for discussion in the committee meeting. It should be read together with the final scope and the external assessment report (EAR).

1. The technology

PillCam COLON 2 (Medtronic) is a type of colon capsule endoscopy (CCE) technology which provides visualisation of the colon for detecting polyps and other abnormal bowel pathology. The capsule is swallowed under clinical supervision following a bowel cleansing routine starting the day before. Additional booster medications are taken after the capsule has been swallowed to help progress it through the colon. The capsule captures images over the course of 10 or more hours, depending on how fast it moves through the colon. The capsule transmits data to a sensor belt that is worn by the patient, or a sensor array that directly attaches directly to the patient for the duration that the capsule is in the body. After the capsule is excreted, the raw data is processed using PillCam desktop software and compiled into a video for review which can be uploaded to the secure PillCam Cloud Reader software. The user, a trained endoscopist, can play, rewind and fast-forward the video whilst marking anatomical landmarks and thumbnails containing images of interest to produce an interpretation that can be summarised in a patient report.

2. The condition

Colorectal polyps are small growths on the inner lining of the colon. Polyps are not usually cancerous. However, some may develop into adenomas which

can be precancerous. People with adenomas have a higher risk of developing colorectal cancer if the adenomas are not removed.

Bowel polyps are very common, affecting about 1 in 4 of the UK population aged 50 or over. Risk factors for colorectal polyps include older age, genetics and family history of bowel polyps or bowel cancer, dietary and lifestyle factors and conditions that affect the gut such as colitis or Crohn's disease. Most bowel polyps do not cause any symptoms, so most people are unaware that they have them. Colorectal cancer is the fourth most common cancer in the UK with approximately 44,000 new cases and around 16,800 deaths per year (Cancer Research UK, 2024). Over half of the people diagnosed with colorectal cancer in England survive at least 10 years after diagnosis and early diagnosis improves survival (Cancer Research UK, 2024). Colorectal polyps are usually picked up during screening for bowel cancer or when the bowel is investigated for another reason.

3. Current practice

Referral on suspected cancer pathway

A suspected cancer pathway referral means an urgent referral directly by the GP after a clinical assessment of symptoms. The referral would be for the most appropriate test or an urgent appointment with a specialist.

Faecal immunochemical testing (FIT) is designed to detect small amounts of blood in a faecal sample by using antibodies specific to human haemoglobin. FIT is recommended by NICE to guide referral in primary care for people with symptoms that may be indicative of colorectal cancer (DG56). The guidance recommends that adults with a FIT result ≥10 µg/g should be referred using a suspected cancer pathway referral, and that adults with a FIT result <10 µg/g should be referred to an appropriate secondary care pathway if there is a strong clinical concern of cancer because of ongoing unexplained symptoms.

Post-polypectomy surveillance

Following findings on a previous colonoscopy, people may be scheduled for a follow up surveillance colonoscopy or colorectal imaging. The British Society

of Gastroenterology guidance on post-polypectomy and post colorectal cancer resection surveillance recommends that people who are at high risk for future colorectal cancer following polypectomy should undergo a one-off surveillance colonoscopy at 3 years.

Diagnosis of colorectal polyps and cancer

Colonoscopy is often used for diagnosing colorectal cancer in people without major comorbidities. It can visualise the entire colon and biopsies can be taken and examined histologically to confirm a diagnosis. Polyps can often be removed as they are identified. Colonoscopy requires preparation of the colon using diet modification and laxatives and is most frequently performed as an outpatient procedure. It is estimated that in around 5% to 20% of people referred for colonoscopy, the procedure cannot be completed, that is, the colon cannot be fully visualised. It is associated with very rare but serious complications, such as perforation of the bowel and heavy bleeding that may require a transfusion.

Because of its invasive nature and the risk of dehydration during colon preparation, colonoscopy may not be suitable for elderly people and those with comorbidities such as kidney disease. For those people, CT colonography is the alternative imaging investigation. People having a CT colonography need to consume a contrast-based material, require air insufflation and are exposed to potentially harmful ionising radiation. The Association of Coloproctology of Great Britain and Ireland/British Society of Gastroenterology guidance recommends that CT colonography is equivalent to colonoscopy for detection of colorectal cancer, and the choice should be determined by local expertise and availability.

Treatment of colorectal polyps and cancer

The most common finding during a colonoscopy is colorectal polyps, which may be removed using cauterisation or a snare. In rare cases, surgery may be needed to treat polyps by removing part of the bowel. After bowel polyps are removed, they are sent for testing in a laboratory. If colorectal cancer is confirmed, NICE guideline (NG151) on colorectal cancer recommends further

imaging tests, such as CT or MRI, to stage the cancer and determine what treatment is needed. Colonoscopy may also find other bowel diseases such as Crohn's disease, ulcerative colitis and diverticulosis, which may need further treatment and follow-up.

4. Unmet need

NHS endoscopy services are under considerable strain and there are long waiting times for colonoscopy for some patients. Clinicians have observed that many people on the suspected colorectal cancer referral pathway have no abnormal pathology found at colonoscopy. CCE could be used as an alternative to colonoscopy to help rule out polyps and colon cancer. CCE may be used as a filter or triage test so that therapeutic colonoscopy can be used for people who need a biopsy or polypectomy. This may help reduce endoscopy service waiting lists and aid early cancer detection by prioritising people who need further tests and treatment.

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope.

5. Decision problem

Table 1 outlines the criteria used by the external assessment group (EAG) when identifying potentially relevant literature for inclusion. For further details, refer to the final protocol.

Table 1 Inclusion criteria

Population	Adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer who are referred to secondary care. Subgroups: • People with a positive FIT score of 10-100µg/g. • People with a negative FIT result of <10µg/g with concerning clinical symptoms. • Adults who are due to have a post-polypectomy surveillance colonoscopy at 3 years because of high-risk findings at their baseline colonoscopy. Subgroups: • People who have declined optical colonoscopy.

	• People who have had an incomplete optical colonoscopy despite adequate bowel preparation. Exclusion criteria: • People with a rectal or anal mass or anal ulceration.
Intervention	• CCE with the PillCam COLON 2 device
Comparator	• Colonoscopy • CT colonography
Outcomes	• Intermediate measures (diagnostic accuracy, completion rates, bowel cleansing level, detection rates, uptake, number of colonoscopies prevented, proportion of follow-up investigations required, number of polyps and cancers missed) • Clinical outcomes (number of colorectal cancer diagnoses, stage of detected cancers, number of other bowel pathologies identified, number of advanced adenomas detected, adverse events, mortality) • Patient-reported outcomes (health related quality of life, anxiety, preferences)

Abbreviations; FIT, faecal immunochemical test; CCE, colon capsule endoscopy.

6. Clinical evidence

The EAG did a comprehensive literature search to identify relevant published clinical evidence. The search and selection methods are in section 3.3.1 and Appendix 2 of the EAR.

6.1 Overview of key studies

Database searches and identification of studies from other sources returned 2468 unique records, 179 of which were sought as full texts for inclusion assessment. As a result, 19 studies reported in 24 papers were included in the clinical evidence review. Due to the scarcity of evidence identified using the criteria outlined in Table 1, these papers included some identified using widened criteria, using a staged approach as outlined in section 3.2 and Appendix 1 of the EAR. This resulted in different inclusion criteria being used for some aspects of the decision problem to include evidence that may not be directly applicable but may support decision making. The papers included in the clinical evidence review were 6 diagnostic test accuracy studies (1 within scope, 5 with widened criteria), 11 diagnostic yield studies and 4 patient preference studies (3 within scope, 1 with widened criteria).

Diagnostic test accuracy

Table 2 summarises the characteristics of the 6 studies reporting diagnostic test accuracy. Most studies included in the evidence review were in mixed populations, that is, they included some patients who were not within the scope of the assessment. Further, the studies did not report accuracy in any of the protocol-defined subgroups, for example, people with a positive FIT score of 10-100µg/g.

Table 2 Study and patient characteristics of studies reporting diagnostic test accuracy (see Table 3 and Table 4 of the EAR for further details)

Author year **Country** **Funding/CoI**	**Study design**	**Number of participants analysed** **% in-scope**	**Inclusion criteria**
Ismail 2021 Ireland No CoI to declare	Prospective, single centre	n=66 100%	Patients referred from primary care for investigation of lower gastrointestinal symptoms, who required a non-urgent colonoscopy based on vetting by a consultant gastroenterologist applying NICE criteria.
Eliakim 2009 Israel Given Imaging	Prospective, multicentre	n=98 41%	Patients scheduled to undergo colonoscopy for either known or suspected colonic disease.
Spada 2011 Europe Given Imaging	Prospective, multicentre	n=109 64%	Patients scheduled to undergo colonoscopy for either known or suspected colonic disease.
Hagel 2014 Germany Given Imaging	Prospective, single centre	n=23 29%	Patients scheduled to undergo colonoscopy for either known or suspected colonic disease.
Morgan 2016 USA Given Imaging	Prospective, multicentre	n=50 Unclear since some patients had more than one indication, possibly 44% (those not undergoing average-risk screening)	Participants with indications for conventional colonoscopy, including clinical symptoms, recent change in bowel habits patients ≥50 years, a polyp ≥10 mm on a prior radiographic test or sigmoidoscopy, a personal history of polyp(s) ≥6 mm in size that was removed at least 3 years ago, or colorectal

			cancer screening if age was ≥60 years.
Omori 2024 Japan Authors had no CoI to declare	Prospective, single centre	n=89 Unclear as category definitions lack detail, potentially as few as 11% or as many as 72%	Faecal immunochemical testing positive patients requiring colorectal tumour screening after upper gastrointestinal tumour detection, suspected colonic lesions based on other investigations, and symptoms such as haematochezia, long-term diarrhoea, or constipation in whom the need for colonic investigation was determined by a physician.

Directly applicable evidence

One study (Ismail 2021) fully met the inclusion criteria set out in the scope, including symptomatic patients as per NICE criteria prior to 2021. Sensitivity and specificity for clinically significant polyps, as defined by European Society of Gastrointestinal Endoscopy criteria, was calculated to be 100% and 98%, respectively. This study was limited due to a small number of intermediate-to-low risk participants (n=66, 7 significant polyps). Furthermore, there was some uncertainty in the threshold used to detect polyps, per-polyp estimates were not reported, and the prevalence of polyps was low (10.6%). Further uncertainty was introduced by risk of bias arising from the interpretation of the CCE and colonoscopy results due to the colonoscopy interpretation not being blinded to the CCE results. This data was deemed insufficient for the EAG's economic model; hence, further data were sought.

Partially applicable evidence

Table 3 shows the diagnostic test accuracy for detecting polyps in mixed populations that included at least some of the patients defined in the NICE scope. These studies included between 64% and potentially as few as 11% within scope, introducing uncertainty in the estimates reported as it is unclear how findings would translate in patients whom CCE would be used in practice. The EAG commented that the differences seen in diagnostic test accuracy by polyp size could reasonably reflect that differences in findings would exist between mixed and in-scope populations due to differences in polyp size and distribution.

Table 3 Pooled sensitivity and specificity estimates of CCE for detecting polyps in mixed populations from the EAG analyses

Polyp size	Number of studies	Sensitivity (95%CI)	Specificity (95%CI)
Any size	2	0.78 (0.51-0.90)	0.60 (0.27-0.88)
≥6mm	4	0.83 (0.70-0.91)	0.69 (0.52-0.81)
≥10mm	4	0.85 (0.70-0.94)	0.90 (0.82-0.95)

The relevance and interpretation of the diagnostic test accuracy data depend on what CCE findings would trigger a referral for colonoscopy. If a polyp threshold of ≥6mm was used, 17% (95% confidence interval [CI] 9 to 30%) of patients with polyps of that size would likely be missed and not referred for colonoscopy. At this threshold, 31% (95%CI 19 to 48%) of participants who do not have a polyp of this size would likley be referred for colonoscopy, despite not needing one. If using a threshold of ≥10mm to trigger colonoscopy referral, the proportion of missed polyps remains similar, but the proportion of unnecessary colonoscopy referrals would be reduced to 10% (95%CI 5 to 18%). However, this strategy would mean that patients that only have polyps <10mm seen on CCE would not be treated, and it is possible that some of these may be adenomatous or cancerous, or may become so over time.

The EAG acknowledged significant between-study clinical heterogeneity, introduced by varied inclusion criteria which resulted in moderate to high statistical heterogeneity being observed. This introduces uncertainty into the generalisability of the diagnostic test accuracy results to the use of CCE in clinical practice. But, the EAG did note low risk of bias for most items, indicating robust methodology. The EAG compared the results of its meta-analyses with other published systematic reviews. Table 20 of the EAR summarises the differences in diagnostic test accuracy results between reviews, with the EAG's analysis resulting in the lowest estimates across all polyp sizes. Differences in results are likely due to differing inclusion criteria, with the EAG's review excluding exclusively screening populations.

Adenomas and colorectal cancer

Data on the diagnostic test accuracy of CCE for adenomas was limited to 1 small study (n=89) with potentially poor generalisability to the decision

problem. Diagnostic test accuracy was poor, except for adenomas ≥10mm, where sensitivity was 0.81 (95% CI 0.65 to 0.91) and specificity was 0.91 (95% CI 0.86 to 0.94). Two studies reported that CCE detected 100% of colorectal cancer cases; however, this was based on very low rates (1 and 3 events).

Diagnostic yield and subsequent testing

Four UK studies reported diagnostic yield in the scope-defined populations. Section 3.3.3 of the EAR shows the numbers of polyps identified for various size categories. The data most relevant to the unmet need and decision problem relates to subsequent tests and discharge rates. The estimates of capacity spared in England and Wales, are as follows: FIT <10µg/g: [redacted], FIT10-100µg/g: [redacted] and 50% and post-polypectomy surveillance: [redacted]. It is unclear how many diagnoses were missed (false negatives) amongst these patients who did not receive a subsequent test.

Upon expanding the inclusion criteria, 7 studies were included in patients who refused or had an incomplete colonoscopy. The proportion of patients within the scope of the assessment ranged from 52% to 74%.The number of colonoscopy referrals post-CCE ranged from 26% to 70% across the studies.

Bowel cleansing rates and completion rates

Across all studies, bowel cleansing rates ranged from 54% to 92%. Bowel cleansing regimens were variable, though most used polyethylene glycol (PEG) and bisacodyl. Completion rates were generally defined as complete visualisation of the colon within battery life and ranged from 40% to 98%. CCE completion rates were most variable in studies of patients with incomplete colonoscopy or who refused colonoscopy, ranging from 40% to 77%, though this category also contained the largest number of studies (n=7). Notably, when including CCEs that completed an incomplete index test colonoscopy, completion rates for combined investigations were between 70% and 98%.

Adverse events, technical failures and retentions

Adverse events were largely related to bowel preparation and were relatively uncommon (usually <5%), though not all studies reported adverse events, and

those that were reported may be only those severe enough to warrant reporting. Technical failures and retentions were not reported by all studies and where they were reported, they were relatively rare (≤3%).

Patient preference

All 4 studies reporting patient preference included symptomatic patients, with 1 study also including surveillance patients, although it was unclear if they met the scope definition of polyp-surveillance populations. Key points of dissatisfaction with CCE included: provision of information, problems with the bowel preparation regimen, pain and discomfort after swallowing the capsule, the wait for results and a subsequent colonoscopy where needed, the impact on daily life of both the bowel preparation regimen and wearing the belt and recorder. Some people liked aspects of CCE, including reduced pain and discomfort compared with colonoscopy and the ability to continue with normal daily activities. Some preferred colonoscopy over CCE in certain clinical situations. CT colonography was generally preferred over CCE. However, studies used different methods to assess preference, and preference for one test over another was not consistent. It is unclear if the findings of the studies are generalisable to post-polypectomy surveillance patients. The EAG noted other limitations in the evidence, namely the population sampling method used, small sample sizes and unclear participant information provision as to the performance and potential for further investigations being required following the tests, all of which may have affected the reported results.

6.2 Ongoing studies

The EAG identified 7 ongoing studies. Of note, the ColoCap study is a diagnostic accuracy study being done in the UK. This study will recruit people with suspected colorectal cancer, inflammatory bowel disease, and post-polypectomy surveillance populations. It is unclear if this study is using the PillCam COLON 2 technology. This study will report outcomes including sensitivity, specificity and patient acceptability for CCE and is likely to be highly relevant to the current decision problem.

7. Health economic evidence

In parallel to the search for diagnostic test accuracy studies, the EAG did a systematic search for existing economic evaluations of CCE in adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer, or in people who are in colonoscopic surveillance. The search returned 229 records, 3 of which are summarised in the assessment report.

Palimaka et al., 2015 is a model-based cost-effectiveness analysis of CCE with PillCam COLON 2 compared with CT colonography in adults with known or suspected colonic disease, done in Canada. Base case results suggest that CCE leads to incremental life years gained (LYG) of 0.000966 at an additional cost of $258.36 per patient tested, resulting in an incremental cost effectiveness ratio (ICER) of $26,751 per LYG (when this calculation was replicated by the EAG, the ICER was $267,000 per LYG, suggesting a reporting error in either the LYG or ICER values). The authors concluded that the model was highly sensitive to changes in the assumptions surrounding the diagnostic accuracy of the 2 tests. Full details and critical appraisal of this evidence is available in section 4.1.2.1. of the EAR.

A cost comparison conducted by the Scottish Health Technologies Group compared locally delivered CCE with the colonoscopy-based diagnostic pathway currently used in Scotland and assumed equivalent diagnostic accuracy between the 2 interventions. The comparison was conducted for 3 separate populations that broadly align with those in the present assessment: 1) people undergoing post-polypectomy surveillance, 2) people with colorectal cancer symptoms and a positive FIT and 3) people with colorectal cancer symptoms and a negative FIT (threshold for positive FIT not specified). In population 1, CCE was cost-incurring at an additional cost of £64.75 per patient, in populations 2 and 3, CCE was cost-saving with savings of £6.71 and £0.36 per patient, respectively. Full details are available in section 4.1.2.2. of the EAR.

The company, Medtronic, submitted an unpublished manuscript that reported on the results of a model-based UK cost comparison and resource use

analysis of CCE for people with symptoms of colorectal cancer who are referred to secondary care with a FIT score of 10-100µg/g. [redacted]

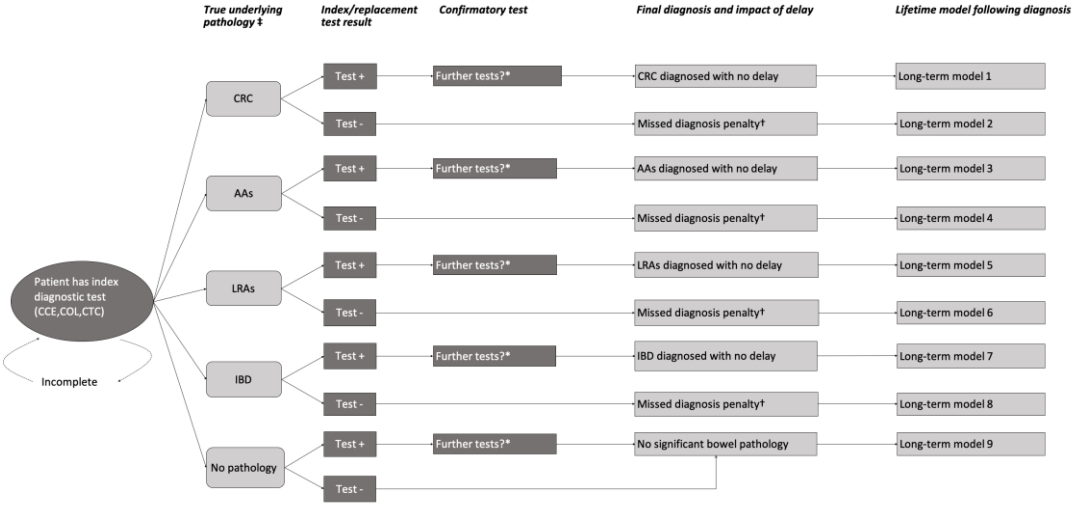
Full details are available in section 4.2. of the EAR.

7.1 Health economic model

The EAG developed a health economic model to assess the incremental cost-effectiveness of CCE versus colonoscopy and CT colonography. The model included a short-term decision tree model and a long-term model to estimate expected lifetime health outcomes and costs according to the patient's true underlying pathology and the results of the index test. For patients with colorectal cancer, advanced adenomas or low-risk adenomas, lifetime health outcomes and costs were based on re-analyses of the MiMiC-Bowel cancer screening model, which was also used to inform NICE's assessment of FIT testing (DG56).

The model begins at the point at which an index test would be done in secondary care. The model defines the true underlying pathology in terms of presence of colorectal cancer, advanced adenomas, low-risk adenomas or inflammatory bowel disease, or for patients with none of these, no significant bowel pathology. The underlying pathologies are mutually exclusive and membership of each is determined by the most advanced colorectal pathology identified. An overview of the model is shown in Figure 1, and further details of the economic modelling are in section 4.3 and Table 26 of the EAR.

Figure 2 General structure of the EAG model



COL - colonoscopy; CTC - computed tomography colonography; CCE - colon capsule endoscopy; CRC - colorectal cancer; LRA - low-risk adenomas; AAs - advanced adenomas; IBD - inflammatory bowel disease
* Following a positive index test, the further tests required will depend on the acceptability of COL and the pathology detected. This may include diagnostic or therapeutic COL (or in some patients, FSIG).
† For patients with underlying colorectal cancer, this penalty is estimated as a potential worsening shift in cancer stage. For people with AAs and LRAs, a penalty is applied to reflect an increased risk of polyp growth or progression to colorectal cancer. For people with IBD, a penalty is applied to reflect potential worsening of disease severity at the point of later diagnosis.
‡ The prevalence of each bowel pathology differs between the populations.
The index test is CCE, COL or CTC. A replacement test is one which is used to replace an incomplete index test, and it may be the same as the index test or a different comparator test. A completed index test or replacement test will give an initial diagnosis. The further tests reflect confirmatory tests which will ultimately provide the correct diagnosis of the underlying bowel pathology, where present.

Population

The populations represented in the economic model represent the 3 groups and 2 subgroups outlined in Table 1. All patients who enter the model are assumed to be fit enough to undergo colonoscopy and to receive subsequent active or palliative treatment for any underlying pathology detected. The model includes separate analyses for people who are willing and able to undergo colonoscopy and people who initially decline colonoscopy.

Intervention and comparator

The intervention is CCE with the PillCam COLON 2, which is assumed to be swallowed under clinical supervision in an outpatient setting, with data interpreted by a trained endoscopist. For the colonoscopy-eligible population, the model includes both CT colonography and colonoscopy as comparators. For the colonoscopy-ineligible population, CT colonography is the only comparator. The model reflects 3 potential uses of the tests:

- index test (the first test that a patient is referred for)
- replacement test (used if the index test fails)
- confirmatory test (used to confirm positive findings from an index or replacement test).

A summary of the comparisons by subgroup are shown in table 4.

Table 4 Summary of the EAG's economic comparisons by subgroup

Analysis No.	Population	Colonoscopy-eligible?	Intervention	Comparators
1a	Symptomatic, FIT 10-100µg/g	Yes	CCE	COL, CTC
1b		No	CCE	CTC
2a	Symptomatic, FIT <10µg/g	Yes	CCE	COL, CTC
2b		No	CCE	CTC
3a	Surveillance (post-polypectomy)	Yes	CCE	COL, CTC
3b		No	CCE	CTC

COL - colonoscopy; CCE - colon capsule endoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test. Analysis marked with 'a' indicate colonoscopy-eligible populations and those marked with 'b' indicate colonoscopy-ineligible populations.

7.2 Model inputs

The key model inputs are summarised in Table 5, and an in-depth explanation of model parameters is available in section 4.3.3. and Table 31 of the EAR. Data from the NHSE CCE Pilot Study was used to inform prevalence, CCE completion rate and use of flexible sigmoidoscopy as a subsequent investigation and is available in Table 32 and Table 33 of the EAR. Where available, systematic reviews and meta-analyses were used to inform other inputs. Where multiple studies were identified, those done in the UK or that aligned with estimates used in the NICE appraisal of FIT to guide colorectal cancer pathway referral in primary care were favoured.

Diagnostic test accuracy

The diagnostic accuracy of each test for detecting individual pathologies is outlined in Table 5. CCE estimates were based on the EAG's meta-analyses and estimates for CT colonography and colonoscopy were based on published systematic reviews and population-based studies. Diagnostic accuracy for each test was assumed to be the same in all 3 populations

included in the scope. The diagnostic accuracy of CCE for detecting low risk adenomas and advanced adenomas was based on estimates from the EAG's meta-analysis for ≥6mm polyps and ≥10mm polyps, respectively. Inadequate data was identified for the sensitivity of CCE for detecting colorectal cancer and inflammatory bowel disease. So, the EAG assumed sensitivity for colorectal cancer to be equivalent to the sensitivity of CCE for detecting ≥10mm polyps, and for inflammatory bowel disease it assumed sensitivity to be equivalent to colonoscopy. Full details of the sources used for each input are provided in Table 35 and section 4.3.3.2. of the EAR.

Table 5 Sensitivity and specificity estimates applied in the model

Pathology	Parameter	Test*	Point estimate	95% CI
CRC	Sensitivity	CCE	0.851	0.703 to 0.939
		COL	0.935	0.931 to 0.939
		CTC	0.912	0.865 to 0.946
AAs	Sensitivity	CCE	0.851	0.703 to 0.939
		COL	0.929	0.860 to 0.971
		CTC	0.912	0.865 to 0.946
LRAs	Sensitivity	CCE	0.830	0.703 to 0.914
		COL	0.867	0.813 to 0.910
		CTC	0.771	0.733 to 0.805
IBD	Sensitivity	CCE	0.892	0.861 to 0.919
		COL	0.892	0.861 to 0.919
		CTC	0.843	0.75 to 0.918
No pathology	Specificity	CCE	0.904	0.817 to 0.974
		COL	Assumed to be 1.0 due to nature of test	
		CTC	0.803	0.777 to 0.828

CRC - colorectal cancer; AA - advanced adenoma; LRA - low-risk adenoma; IBD - inflammatory bowel disease; CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; CI - confidence interval. * Where FSIG is used as a replacement test, it is assumed to have diagnostic accuracy equivalent to COL

Prevalence

The prevalence of significant underlying bowel pathologies was informed by data from the NHSE CCE pilot study. Participants in this study only received a subsequent test when significant bowel pathology was detected by CCE. This means that diagnostic yield was reported, which may include false positives

and exclude false negatives from the polyp, colorectal cancer and inflammatory bowel disease estimates. Equally, estimates of no significant bowel pathology may include false negatives and exclude false positives. The NHSE CCE pilot study also provided data on the final diagnosis of the subset of patients who were referred for further investigation. This dataset adjusts for false positives arising from the initial CCE, but does not include false negatives who were not referred for further luminal investigation after the index CCE. To account for the limitations of the data reported in the study, the EAG applied a number of adjustments that are described in section 4.3.3. of the EAR. The estimates applied in the EAGs model are shown in Table 6.

Table 6 Estimated true underlying prevalence applied in the model

CCE-indicated pathology	Symptomatic FIT 10-100µg/g		Symptomatic FIT <10µg/g		Surveillance	
	Number	Proportion	Number	Proportion	Number	Proportion
CRC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10mm polyps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<10mm polyps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

FIT - faecal immunochemical test; CRC - colorectal cancer; IBD - inflammatory bowel disease; NSBP - no significant bowel pathology

Completion and complication rates

The model assumes that all patients with an incomplete CCE or CT colonography would be offered a different test, regardless of the reason for the index test being incomplete. To avoid an overly complex model, it also assumes that only the index test can be incomplete and that all subsequent tests will be complete. Estimates of CCE completion rates were taken from the NHSE CCE Pilot Study. CT colonography and colonoscopy completion rates were taken from a systematic review and retrospective patient experience study, respectively.

The model includes risks of complications both index and subsequent tests. Perforation is included as a possible complication of both colonoscopy and CT colonography. Increased lifetime colorectal cancer risk due to exposure to ionising radiation is included as a complication for CT colonography only. Bleeding is included as a complication for colonoscopy only. Capsule retention and aspiration are included as complications of CCE. A summary of completion and complication rates and the complication-associated QALY losses is included in Table 7. Further details on the sources used for are available in Table 36, Table 37 and Table 38 of the EAR.

Costs

The cost of each complete diagnostic test applied in the model is summarised in Table 7. A breakdown of the costs associated with CCE was provided by the company, Medtronic, and is shown in Table 42 of the EAR. Costs of diagnostic and therapeutic colonoscopy, CT colonography and flexible sigmoidoscopy, and costs of managing complications were taken from NHS reference costs 2022/2023.

Health-related quality of life, mortality and costs

Key model parameters are summarised in Table 7. A full description of the parameters and sources used is available in section 4.3.3. of the EAR.

Table 7 Key model parameters

Parameter	Point estimate (95% confidence interval)
Completion rate – CCE	[redacted]
Completion rate – COL	0.92 (0.91-0.92)
Completion rate – CTC	0.98 (0.96-1.00)
Probability of CCE complications (aspiration, retention)	Aspiration: 0.001 (0.001 to 0.002) Retention: 0.0064 (0.0040 to 0.0093)
Probability of COL complications with polypectomy	Bleeding: 0.0098 (0.0077 to 0.0121) Perforation: 0.0008 (0.0006 to 0.0010)
Probability of COL complications without polypectomy	Bleeding: 0.0006 (0.0002 to 0.0011) Perforation: 0.0004 (0.0002 to 0.0008)

Probability of COL mortality (same for with and without polypectomy)	0.00003 (0.00001 to 0.00006)
Probability of CTC complications	Perforation: 0.0004 (0.0000 to 0.0010) Colorectal cancer risk due to radiation: [redacted]
QALY losses due to test complications	Perforation (COL and CTC): 0.0025 Bleeding (COL): 0.0014 CRC due to radiation (CTC): 4.19 Capsule retention (CCE): 0.0092 Capsule aspiration (CCE): 0.00
Total cost per CCE, COL, CTC or FSIG procedure completed	CCE (with underlying colorectal cancer): £1,005 CCE (with underlying pathology other than colorectal cancer): £811 Diagnostic COL (with underlying colorectal cancer): £1,245 Diagnostic COL (with underlying pathology other than colorectal cancer): £1,051 Therapeutic COL: £1,087 CTC (with underlying colorectal cancer): £492 CTC (with underlying pathology other than colorectal cancer): £298 FSIG: applied as reduction in procedure cost of £131 relative to diagnostic COL
Cost of managing complications	Bleeding (COL): £1,897 Perforation (COL and CTC): £8,120 Aspiration (CCE): £2,908 Retention - detection (CCE): £41 Retention - capsule location (CCE): £142 Retention - management (CCE): £4,164 Lifetime cost associated with radiation-related colorectal cancer (CTC): £29,919
Long-term model 1 (colorectal cancer, no delay)	**Symptomatic** QALYs: 7.31 Costs: £29,919 **Surveillance** QALYs: 9.32 Costs: £32,199
Long-term model 2 (colorectal cancer, with delay)	**Symptomatic** QALYs: 6.71 Costs: £28,222 **Surveillance** QALYs: 7.77 Costs: £24,186
Long-term model 3 (advanced adenomas, no delay)	**Symptomatic** QALYs: 11.50 Costs: £521 **Surveillance** QALYs: 10.93 Costs: £661
Long-term model 4 (advanced adenomas, with delay)	**Symptomatic** QALYs: 11.34 Costs: £3,259 **Surveillance** QALYs: 10.31 Costs: £5,878
Long-term model 5 (low risk adenomas, no delay)	**Symptomatic** QALYs: 11.50 Costs: £0 **Surveillance** QALYs: 10.93 Costs: £190

Long-term model 6 (low risk adenomas, with delay)	**Symptomatic** QALYs: 11.48 Costs: £292 **Surveillance** QALYs: 10.86 Costs: £745
Long-term model 7 (inflammatory bowel disease, no delay)	**Symptomatic** QALYs: 10.28 Costs: £78,202 **Surveillance** QALYs: 9.77 Costs: £75,118
Long-term model 8 (inflammatory bowel disease, with delay)	**Symptomatic** QALYs: 10.22 Costs: £79,057 **Surveillance** QALYs: 9.71 Costs: £75,973
Long-term model 9 (no significant bowel pathology)	**Symptomatic** QALYs: 11.50 Costs: £0 **Surveillance** QALYs: 10.93 Costs: £0

CCE - colon capsule endoscopy; CTC - computed tomography colonography; QALY - quality-adjusted life year; FSIG, flexible sigmoidoscopy

7.3 Model results

Base case

In patients who are willing to undergo colonoscopy (COL-eligible), fully incremental probabilistic base case results from the EAG model suggest that CCE generated fewer QALYs and had greater costs than colonoscopy in all populations, resulting in it being dominated. CT colonography is expected to be less effective and less expensive than colonoscopy in all populations and is estimated to generate slightly more QALYs than CCE in the surveillance population.

In patients who initially decline colonoscopy (COL-ineligible), fully incremental probabilistic base case results suggest that CCE is expected to be dominated by CT colonography in the symptomatic FIT 10-100µg/g and surveillance populations. In the symptomatic FIT <10µg/g population, the model suggests that CCE generates slightly more QALYs and incurs higher costs compared with CT colonography; the ICER is expected to be greater than £713,000 per QALY gained. Fully incremental analysis results are in Table 46 and Table 47 in section 4.3.6 of the EAR.

In pairwise probabilistic analyses, CCE was dominated by colonoscopy in all populations. When compared with CT colonography, CCE was either dominated or had an ICER of £467,706 or higher per QALY gained, in all populations. Pairwise results are in Appendix 11 of the EAR; tables 70 and 71

show the comparison between CCE and colonoscopy and tables 72 and 73 show the comparison between CCE and CT colonography.

Scenario analyses

The EAG did 27 deterministic sensitivity analyses to explore uncertainties in the base case. A full list of the scenarios tested is available in section 4.3.4 of the EAR. In pairwise scenario analyses when compared with colonoscopy across all populations, CCE was either dominated or had an ICER of £389,765 or higher per QALY gained. When compared with CT colonography across all populations, CCE was either dominated or had an ICER of £32,868 or higher per QALY gained. The EAG included 1 scenario analysis that was considered the most optimistic scenario, combining a CCE completion rate of 85% and assuming equal diagnostic accuracy between CCE and colonoscopy. In all populations, an ICER well above NICE's threshold range of £20,000 to £30,000 was calculated with the lowest ICER being £71,176 per QALY gained in colonoscopy-eligible post-polypectomy surveillance populations when compared with CT colonography (in pairwise analysis). Pairwise sensitivity analyses are in tables 74 and 75 in Appendix 11 of the EAR. Fully incremental results of the deterministic sensitivity analysis are in tables 52 and 53 in section 4.3.6.4 of the EAR.

Intermediate outcomes

In patients who are willing to undergo colonoscopy (COL-eligible), the model suggests that CCE would lead to substantial reductions in the number of colonoscopies required, compared with colonoscopy; approximately 50%, 46% and 32% in symptomatic patents with a FIT <10µg/g, symptomatic patients with a FIT 10-100µg/g and surveillance populations, respectively. Compared with CT colonography, CCE is estimated to lead to an increase in subsequent colonoscopies and flexible sigmoidoscopies. In patients who initially decline colonoscopy (COL-ineligible), the model suggests that CCE will lead to a small reduction in the number of people being referred for colonoscopies compared with CT colonography; approximately, 8%, 10% and 2% in the symptomatic FIT 10-100µg/g, symptomatic FIT <10µg/g and surveillance populations, respectively. These estimates are based on the

assumption that all patients with an incomplete index test will require colonoscopy or flexible sigmoidoscopy, and the significantly lower probability that CT colonography will be incomplete (2%) compared with CCE ([redacted]).

In terms of pathology detected and missed in the COL-eligible population, CCE is predicted to miss more polyps and colorectal cancer compared with colonoscopy. Compared with CT colonography, the model indicates that CCE will lead to more low-risk adenomas being detected and more advanced adenomas and colorectal cancer being missed in both the COL-eligible and the COL-ineligible populations.

8. Equality considerations

The final scope and the scoping equality impact assessment describe equality considerations for this assessment. The EAG did not identify additional equality issues. There were no data on whether socioeconomic characteristics or ethnicity may impact patient preference, or other outcomes in this assessment.

9. Key points, limitations and considerations

9.1 Clinical evidence

Key points

Diagnostic accuracy

- Data on the diagnostic accuracy of CCE in populations within the scope was limited to a single study. This study reported sensitivity of 1.00 (95%CI 0.65-1.00) and specificity of 0.98 (95%CI 0.91-1.00) for clinically significant polyps in symptomatic patients referred according to NICE criteria at the time of the study.
- Pooled sensitivity and specificity estimates of CCE from studies containing mixed populations were:
  - polyps of any size, 0.78 (95% CI: 0.51-0.90) and 0.60 (95% CI: 0.27-0.88)
  - ≥6mm polyps 0.83 (95% CI: 0.70-0.91) and 0.69 (95% CI: 0.52-0.81)

- ≥10mm polyps 0.85 (95% CI: 0.70-0.94) and 0.90 (95% CI: 0.82-0.95)

Intermediate outcomes

- In people that had an incomplete colonoscopy, CCE completed colonic assessment in between 70% and 98% of cases.

Patient preference

- Patient preference studies reported contrasting preferences. CT colonography was generally preferred over CCE. Some people liked aspects of CCE, including reduced pain and discomfort compared with colonoscopy and the ability to continue with normal daily activities. Some preferred colonoscopy over CCE in certain clinical situations.

Limitations

Diagnostic accuracy

- Diagnostic accuracy data that included a population fully within the scope (symptomatic patients) was limited to a single study containing a small number of intermediate-to-low risk participants.
- Diagnostic accuracy data from studies containing mixed populations is not directly applicable to any of the specific populations outlined in Table 1. Diagnostic accuracy may vary by polyp size, and polyp size distribution may vary between populations, introducing uncertainty in the accuracy estimates that have been generalised to the broader population in this evaluation. It is unclear if this means the results of this evaluation under or overestimate diagnostic accuracy.

Patient preference

- Data for surveillance populations was limited. No studies included solely surveillance populations, and the majority included only symptomatic patients.
- It was unclear if participants were informed of the likelihood of requiring a subsequent colonic investigation following CCE, which may alter perspectives on the acceptability of the test.

Considerations for committee

Diagnostic accuracy

- Does the single study reporting diagnostic accuracy in directly applicable populations provide evidence that CCE may be a suitable alternative to colonoscopy to identify bowel pathology?
- Do the pooled estimates of diagnostic accuracy in mixed populations provide evidence that CCE may be a suitable test to identify bowel pathology in the broad population of people undergoing colonic investigations?
- The ColoCap study is estimated to complete in September 2027. The EAG sensitivity analyses tested different diagnostic accuracy estimates for the 3 tests, including assuming equal diagnostic accuracy of CCE, colonoscopy and CT colonography. All analyses showed CCE being dominated or having a high ICER. Does the committee think additional diagnostic accuracy data for CCE that is specific to the populations described in the scope will help to inform future decision making?

Intermediate outcomes

- Does the potential for CCE to provide complete colonic assessment in people that had an incomplete colonoscopy support its use in the NHS?

Patient preference

- Preference and satisfaction data for CCE compared with colonoscopy and CT colonography were mixed. It may be that this varies depending on individual and medical circumstances. Are there any subgroups that may benefit more from increased choice? Should future research be qualitative to understand potential barriers and facilitators in the use of CCE?

9.2 Health economic evidence

Key points

- In the base case and in all sensitivity analyses, in all populations, CCE was either dominated or had an ICER well above NICE's threshold range of £20,000 to £30,000 per QALY gained compared with colonoscopy or CT

colonography. This suggests that routine adoption of CCE would result in increased costs and reduced societal health.

- The higher costs of CCE compared with colonoscopy and CT colonography are largely due to the need for subsequent tests when CCE is incomplete, or if significant bowel pathology is found.
- CCE generates fewer QALYs than colonoscopy in all populations, and in most populations when compared with CT colonography. The only population where CCE generated more QALYs than CT colonography was in symptomatic patients with a FIT <10µg/g. The reasons for this are:
  - CCE is assumed to have lower diagnostic accuracy than both colonoscopy and CT colonography for colorectal cancer and advanced adenomas.
  - CCE is assumed to have better diagnostic accuracy than CT colonography for low-risk adenomas.
  - [redacted]
  - Complication rates associated with tests (both the index test and subsequent tests) impact on QALYs.

Limitations

- There were inconsistencies in the definition of polyp risk groups between evidence sources. Diagnostic accuracy estimates for some bowel pathologies had to be assumed to be equivalent to estimates for other pathologies or tests, introducing uncertainty into the estimates used. There was also uncertainty in the diagnostic accuracy estimates of colonoscopy and CT colonography, introducing further uncertainty into the diagnostic accuracy inputs. However, the sensitivity analyses of alternative diagnostic accuracy estimates explored these uncertainties and found that CCE remained unlikely to be cost-effective, even when diagnostic accuracy was assumed to be equivalent between tests.
- Assumptions were made on prevalence estimates from the NHSE pilot CCE study due to not doing follow-up colonoscopies in CCE-negative

participants, meaning false negatives could not be ascertained. This meant that prevalence was based on the number of true positives identified and may underestimate the true prevalence of underlying pathologies in the study.

Considerations for committee

- Are the economic model structure, assumptions and clinical and cost parameters suitable to answer the decision question (see final scope) for this assessment?
- Are there any other potential system benefits that are not captured by the economic model, and are these likely to generate improvements in QALYs in other areas of the NHS?

9.3 Colonoscopy sparing

Key points

- The identified clinical evidence reported reductions in colonoscopy estimates for populations meeting the scope criteria of: FIT <10µg/g: [redacted] FIT 10-100µg/g: [redacted] and 50%, post-polypectomy surveillance: [redacted]
- No data was identified in populations within scope that refused or had an incomplete colonoscopy. Data from mixed populations showed that 22% to 76% of participants underwent further tests or procedures after CCE, with 26% to 70% being referred for colonoscopy.
- Economic modelling by the EAG showed that CCE is expected to lead to substantial reductions in the number of colonoscopies required, especially in colonoscopy-eligible symptomatic populations. The main population where waiting times are problematic is the symptomatic with a FIT <10µg/g, as this group is not covered by the 28-day Faster Diagnosis Standard. The [redacted] Additionally, the sensitivity analysis that modelled the impact of halving waiting times for colonic investigation from 8 to 4 months in symptomatic patients with FIT <10µg/g for CCE had no impact on the model results.

- It is unclear how the potential capacity sparing effect of CCE on colonoscopy services may affect QALYs and costs for people undergoing investigations for conditions beyond those included in the EAG model.

Considerations for committee

- Is the reduction in the number of colonoscopies being done assumed in the model realistic, and in practice would this result in capacity sparing? (endoscopist still must interpret the CCE recording, which takes a similar length of time to a colonoscopy)
- Could the colonoscopy-service capacity sparing effect of CCE reduce waiting list times for colonoscopy, particularly in the group of people with symptoms and a FIT score <10µg/g who are not covered by the 28-day Faster Diagnosis Standard?
- Could the reduction in the number of colonoscopies required free up endoscopy services for investigation of conditions beyond those included in this assessment?

9.4 Implementation

- The optimal setting for CCE delivery is unknown. The base case assumed that the CCE capsule would be swallowed under clinical supervision in secondary care. Swallowing the capsule in primary care may help to reduce costs, and this was explored in sensitivity analyses. The alternative setting for delivery of the capsule did not impact on the direction of the results, with CCE remaining dominated by colonoscopy or having a very high ICER compared with CT colonography.
- It was beyond the scope of the assessment to determine the optimal bowel cleansing regimen. Further research into CCE cleansing regimens may improve test completion rates and reduce costs through fewer people requiring subsequent colonoscopy following incomplete CCE. The EAG modelled 100% completion rates for CCE in a sensitivity analysis. This did not impact the direction of the results, with CCE remaining dominated by colonoscopy or having a very high ICER compared with CT colonography.
- Developments in technology may allow images to be interpreted using artificial intelligence, potentially reducing the costs and increasing the

diagnostic accuracy of all colonic investigations. This was beyond the scope of this assessment but is under consideration by NICE in an assessment of artificial intelligence software to help detect and characterise colorectal polyps.

Appendix A: Abbreviations

AA	Advanced adenoma
CCE	Colon capsule endoscopy
CI	Confidence interval
CoI	Conflict of interest
COL	Colonoscopy
CRC	Colorectal cancer
CT	Computerised tomography
CTC	CT colonography
EAG	External assessment group
EAR	External assessment report
FIT	Faecal immunochemical testing
FSIG	Flexible sigmoidoscopy
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
LRA	Low-risk adenoma
LYG	Life years gained
MRI	Magnetic resonance imaging
NHSE	NHS England
NSBP	No significant bowel pathology
PEG	Polyethylene glycol
QALY	Quality-adjusted life year

Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence – Diagnostics Assessment Report

PillCam COLON 2 for investigation of the colon through direct visualisation

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Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Tappenden led the project and was responsible for day-to-day management. Mark Clowes designed and ran the search strategy. Sue Harnan, Gamze Nalbant and Abdullah Pandor conducted the systematic review of the clinical effectiveness data. Sarah Ren designed and undertook the statistical synthesis. Paul Tappenden and Aline Navega Biz undertook the review of published economic evaluations. Mon Mon Yee, Paul Tappenden and Aline Navega Biz critiqued the manuscript describing the company's model and designed and implemented the EAG's health economic model. Chloe Thomas, Laura Heathcote and Sophie Whyte undertook additional analyses using the MiMiC-Bowel screening model. Matthew Kurien, Kevin Monahan and Janine Tappenden provided clinical advice throughout the project. All authors were involved in drafting and commenting on the final report.

SUMMARY OF CHANGES MADE TO THE REPORT FOLLOWING CONSULTATION

Section number	Page number	Change made	Reason for change
Scientific summary	13	Changed "A systematic review was conducted to identify evidence on the clinical effectiveness, diagnostic accuracy and safety of CCE using PillCam COLON 2." To "A systematic review was conducted to identify evidence on the clinical effectiveness, diagnostic accuracy, safety and patient preference of CCE using PillCam COLON 2."	To correct the omission of "patient preference"
Scientific summary	15	Changed "0.75 (95% credible interval [CrI]: 0.51, 0.90)" To "0.78 (95% credible interval [CrI]: 0.51, 0.90)"	To correct a typo
3.3.3.1	68	Changed "The Wales Pilot Study[34] appears to have recruited patients with symptoms and a FIT of <10µg/g, designated "low-risk", but it was not clear if, they were recruited using NG12 criteria." To "The Wales Pilot Study[34] appears to have recruited patients with symptoms and a FIT of <10µg/g, designated "low-risk", and it was likely, based on suggested criteria in the pilot study documentation,[83]"	New information highlighted by the company
3.3.3.1, Table 13	70	Changed "FIT <10µg/g, persistent symptoms "low risk" group" To "FIT <10µg/g, persistent symptoms "low risk" group, likely recruited according to NG12 criteria"	
3.4 Discussion Table 22	105	Changed • Sens 0.75 (0.51-0.90) To • Sens 0.78 (0.51-0.90)	To correct a typo
5.1.1	185	Changed 0.75 (95% CrI: 0.51-0.90) To 0.78 (95% CrI: 0.51-0.90)	
Appendix 1, Table 54	209	Removed "**Bond 2023 (ScotCap)[66]"** from row 3 because it is correctly listed in the final row	Cut and paste error

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Abbreviations

2WW	Two Week Wait
5G	Fifth generation
A&E	Accident and Emergency
AA	Advanced adenoma
AACR	American Association for Cancer Research
ACPGBI	Association of Coloproctology of Great Britain and Ireland
AE	Adverse event
AI	Artificial intelligence
AJCC	American Joint Committee on Cancer
APDW	Asian Pacific Digestive Week
ASCO	American Society of Clinical Oncology
BCSP	Bowel Cancer Screening Programme
BSG	British Society of Gastroenterology
CAN	Canadian
CCE	Colon capsule endoscopy
CD	Crohn's disease
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CODA	Convergence diagnosis and output analysis
CoI	Conflict of interest
COL	Colonoscopy
COVID-19	Coronavirus Disease 19
CRC	Colorectal cancer
CrI	Credible interval
CT	Computed tomography
CTC	Computed tomography colonography
DDW	Digestive Diseases Week
DG	Diagnostics Guidance
DSA	Deterministic sensitivity analysis
DTA	Diagnostic test accuracy
EAG	External Assessment Group
EMR	Endoscopic mucosal resection
EQ-5D-3L	Euroqol 5-Dimenions 3-Level
ER	Emergency room
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
FAP	Familial adenomatous polyposis
FDS	Faster Diagnosis Standard
FIT	Faecal immunochemical test
FN	False-negative
FOBT	Faecal occult blood test
FP	False-positive

FSIG	Flexible sigmoidoscopy
GCS	Gloucester Comfort Scale
GI	Gastrointestinal
GP	General Practitioner
HCRU	Health care resource use
HES	Hospital Episode Statistics
HNPCC	Hereditary non-polyposis colorectal cancer
HRA	High-risk adenoma
HRQoL	Health-related quality of life
HSE	Health Survey for England
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICER	Incremental cost-effectiveness ratio
ICES	Institute for Clinical Evaluative Sciences
IMTO	Innovative Medical Technology Overview
INAHTA	International Network of Agencies for Health Technology Assessment
LED	Light emitting diode
LNPCP	Large non-pedunculated colorectal polyp
LRA	Low-risk adenoma
LY	Life year
LYG	Life year gained
MCMC	Markov Chain Monte Carlo
MDT	Multidisciplinary team
MiMiC-Bowel	Microsimulation Model in Cancer of the Bowel
MMAT	Mixed Methods Appraisal Tool
MRI	Magnetic resonance imaging
N/a	Not applicable
NaP	Sodium phosphate
NCRAS	National Cancer Registration and Analysis Service
NED	National Endoscopy Database
NG	NICE Guideline
NHS EED	NHS Economic Evaluation Database
NHSCII	National Health Service Cost Inflation Index
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
NSBP	No significant bowel pathology
PCCRC	Post-colonoscopy colorectal cancer
PEG	Polyethylene glycol
PET	Positron emission tomography
PHE	Public Health England
PrI	Prediction interval
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses

PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
RCT	Randomised controlled trial
SCHARR	Sheffield Centre for Health and Related Research
SD	Standard deviation
SE	Standard error
SHTG	Scottish Health Technologies Group
SLR	Systematic literature review
SROC	Summary receiver operating characteristic
SWAR	Study Within A Review
TN	True-negative
TNM	Tumour Node Metastasis
TP	True-positive
UC	Ulcerative colitis
UEGW	United European Gastroenterology Week
US	Ultrasound
VAS	Visual analogue scale
VAT	Value Added Tax
WHO-ICTRP	World Health Organization International Clinical Trials Registry Platform
WTP	Willingness-to-pay

Plain English Summary

Bowel cancer is the fourth most common cancer in England. Most bowel cancers start as small growths on the lining of the bowel called polyps. Some polyps can become cancerous over time. If polyps are found and removed before they become cancerous, bowel cancer can be prevented. People with symptoms of bowel cancer are usually sent for a procedure called a colonoscopy, where a small camera with a light is inserted into the colon through the anus. Polyps can be removed, or a tissue sample can be taken. However, waiting times for colonoscopy are long and the procedure is unpleasant. Also, some people may need a different investigation if they are frail, have other illnesses or refuse colonoscopy. PillCam COLON 2 is an alternative procedure which involves swallowing a capsule containing two tiny cameras and a light. It takes pictures inside the bowel and sends them to a computer. However, people may still need to have a colonoscopy afterwards if polyps are found or if PillCam COLON 2 does not fully work. This assessment looks at PillCam COLON 2 as an alternative to colonoscopy and another procedure called computed tomography colonography.

We looked for evidence on the accuracy and acceptability of PillCam COLON 2. We also looked at studies which have used this test in practice. Our review found that PillCam COLON 2 might miss some polyps compared to colonoscopy, but it can avoid further investigations in some patients. Some patients preferred PillCam COLON 2, but others preferred different procedures. Our assessment also looked at whether PillCam COLON 2 represents good value for money for the NHS through cost-effectiveness analyses. The analyses suggest that it is less effective and more expensive than colonoscopy. However, it could help free up constrained colonoscopy services, particularly in people with symptoms of bowel cancer.

1. SCIENTIFIC SUMMARY

1.1 Background

Colorectal cancer (CRC), which is also known as bowel cancer, is the fourth most common cancer and the second most common cause of cancer deaths in England. Most cases of CRC arise from a prior adenomatous polyp in the lining of the bowel through a process known as the adenoma-carcinoma sequence. Colorectal polyps are very common, and the vast majority of polyps do not turn into cancer. The removal of adenomatous polyps interrupts the adenoma-carcinoma sequence and can reduce the risk of developing CRC and can improve survival. The gold standard diagnostic test for the investigation and diagnosis of colorectal polyps and CRC is colonoscopy (COL). COL allows for the detection and removal of colorectal polyps and, if cancer is suspected, a biopsy can be taken as part of the procedure. However, waiting times for COL are long for some patients. In addition, some people are unwilling or unable to undergo COL and require a different luminal investigation such as computed tomography colonography (CTC). This External Assessment Group (EAG) report assesses the use of colon capsule endoscopy (CCE) using PillCam COLON 2 for the investigation of the bowel through direct visualisation. CCE may provide an alternative to COL or CTC to rule out polyps or CRC or may be used as a filter or triage test prior to COL.

1.2 Objectives

The main research question addressed in this report is: *"Does the use of colon capsule endoscopy in adults with lower gastrointestinal signs or symptoms suggestive of CRC, or those due to have post-polypectomy surveillance 3 years after their index colonoscopy represent a clinically and cost-effective use of NHS resources, taking into consideration potential colonoscopy capacity constraints?"*

The objectives of the assessment are as follows:

- To conduct a systematic review of the published evidence on the effectiveness and cost-effectiveness of PillCam COLON 2 for detecting colorectal polyps and CRC
- To develop a health economic model to assess the cost-effectiveness of PillCam COLON 2 compared with COL and CTC from the perspective of the NHS and Personal Social Services (PSS).

1.3 Methods

Clinical effectiveness methods

A systematic review was conducted to identify evidence on the clinical effectiveness, diagnostic accuracy, safety and patient preference of CCE using PillCam COLON 2. The methods for the review were registered on PROSPERO (registration number CRD42024586405). Searches were conducted across six bibliographic databases and the last ten years of eight conference proceedings in August

2024. Reference lists of existing reviews were checked. Studies were included under the following criteria: Population: patients with lower GI signs or symptoms suggestive of CRC, or those due to have post-polypectomy surveillance 3 years after their baseline COL; Intervention: PillCam COLON 2; Study design: randomised controlled trials (RCTs), or a diagnostic test accuracy study with a reference standard of COL (or other reference standards if none were available using COL), or a patient preference or health-related quality of life (HRQoL) study. Relevant outcomes included sensitivity and specificity for detecting polyps (<6mm, 6-9mm, ≥10mm), adenomas and CRC, prevalence, test uptake, bowel cleansing levels, completion rates, other pathologies detected, adverse events (AEs) and patient preference. Due to a lack of evidence, the review inclusion criteria were widened to include studies that recruited other patients as well as those defined in the NICE scope ("mixed" populations), and studies reporting on diagnostic yield as either the number of positive CCE tests (i.e., true-positives [TPs] plus false-negatives [FNs]), or the number of CCE tests confirmed by subsequent COL (i.e., TPs only).

Title and abstract screening was conducted independently by two reviewers. Full text screening was conducted by one reviewer and includes were confirmed by a second reviewer. Data extraction and quality assessment were conducted by one reviewer and checked by a second reviewer. Diagnostic test accuracy study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool and for patient preference studies the Mixed Methods Appraisal Tool (MMAT) was used. Narrative synthesis was conducted for study and patient characteristics and all outcomes. Statistical synthesis used Bayesian methods to pool estimates of sensitivity and specificity where two or more studies reported test accuracy data for a given category of bowel pathology. Sensitivity analyses were conducted excluding studies with high clinical heterogeneity and to test the effect of using a non-informative prior.

Cost-effectiveness methods

The EAG undertook a systematic review of published economic analyses of PillCam COLON 2 versus other diagnostic tests for the detection of colorectal polyps or CRC in people with symptoms of CRC and/or in people who are due to have a post-polypectomy surveillance COL. The EAG also critically appraised an unpublished manuscript describing a model-based cost and resource use analysis of CCE versus COL and CTC for detecting colorectal polyps and CRC submitted to NICE by the test manufacturer (Medtronic Ltd.).

The EAG developed a *de novo* economic model to assess the incremental cost-effectiveness of CCE using PillCam COLON 2 versus COL and CTC in the three main analysis populations listed in the NICE scope: (i) people with symptoms suggestive of CRC with a faecal immunochemical test (FIT) score of 10-100µg/g; (ii) people with symptoms suggestive of CRC with a FIT score of <10µg/g and (iii) people who are due to have a post-polypectomy surveillance COL at 3-years because of high-risk

findings at their baseline COL. Separate analyses were conducted within each analysis population to reflect differences in diagnostic pathways for people who are willing and able to undergo COL and for people who initially decline COL (denoted as "COL-eligible" and "COL-ineligible" subgroups, respectively). The diagnostic pathways included in the model were informed by clinical opinion and long-term outcomes and costs were estimated through re-analyses of the Microsimulation Model in Cancer of the Bowel (MiMiC-Bowel) screening model. Key model parameters were informed by the National Health Service England (NHSE) CCE Pilot Study, meta-analyses of the diagnostic accuracy of CCE, CTC and COL, systematic reviews of test complications, routine costing sources, other literature and assumptions. Sensitivity analyses were conducted to explore the impact of alternative assumptions and evidence sources on the model results.

1.4 Results

Database searches retrieved 2,376 records, whilst other search methods retrieved 92 records. After widening of the inclusion criteria, the review included three evidence types: (i) diagnostic test accuracy studies in scope-defined populations (n=1 study) or mixed populations (n=5 studies) to provide evidence on the sensitivity and specificity of CCE; (ii) diagnostic yield studies to provide estimates of underlying disease prevalence and capacity spared (n=4 in scope-defined populations; n=7 in mixed populations with incomplete COL or who refused COL), and (iii) patient preference studies (n=4 studies). In total, 19 studies reported across 24 sources were included. Two studies contributed data to two evidence types (yield studies in the correct population and patient preference).

Diagnostic test accuracy studies: One diagnostic test accuracy study conducted in a scope-defined symptomatic population was included. Sensitivity and specificity for clinically significant polyps were calculated by the EAG to be 100% (95% confidence interval [CI]: 0.65-1.00) and 98% (95% CI: 0.91-1.00), respectively, but the study was small (n=66, 7 significant polyps) and it probably did not include the full spectrum of relevant symptomatic patients. Five diagnostic test accuracy studies conducted in mixed populations were also included. The proportion of patients within the scope of the assessment in these studies ranged from 11% to 64%. Four studies reported data suitable for pooling in the statistical synthesis. Pooled sensitivity and specificity for polyps of any size (n=2) were 0.78 (95% credible interval [CrI]: 0.51, 0.90) and 0.60 (95% CrI: 0.27, 0.88), respectively; for polyps ≥6mm (n=4) 0.83 (95% CrI: 0.70, 0.91) and 0.69 (95% CrI: 0.52, 0.81), respectively; and for ≥10mm (n=4) 0.85 (95% CrI: 0.70, 0.94) and 0.90 (95% CrI: 0.82, 0.95), respectively. Data on the diagnostic test accuracy for adenomas was limited to one small study (n=89) with potentially poor generalisability to the decision problem due to the low proportion of patients in the study who were within the scope of the assessment (11%).

Diagnostic yield studies: Four studies reported on diagnostic yield in the scope-defined populations. They reported the numbers of polyps identified, but the data of perhaps most interest relate to

subsequent tests and discharge rates, where COL was spared in 50% to 37% (n=3 studies) of symptomatic patients. In scope-defined surveillance patients (3-year post-polypectomy), COL was spared in [redacted] of patients. Seven studies were included in patients who refused or had an incomplete COL in mixed populations. The proportion within the scope of the assessment ranged from 52% to 74%. The proportion of COL referrals post-CCE ranged from 26% to 70% across the studies. When including CCEs that completed incomplete COLs in the completion rate, it ranged from 70% to 98%.

Patient preference studies: Four studies of patient preference were included. Three were conducted in symptomatic patients, and one in both symptomatic and surveillance populations, but some were under surveillance for reasons other than having undergone a previous polypectomy. Patient preference studies showed that patients varied in their opinions. Overall, there was general satisfaction with CCE (e.g., comfort, convenience, communication and friendly staff), and some evidence that patients were most satisfied with CTC, but more satisfied with CCE compared to COL. Dissatisfaction centred around the bowel preparation, pain after swallowing the capsule, the wait for CCE results and a subsequent COL where necessary, the impact on daily life (bowel preparation and wearing the belt/recorder), and aspects of patient information. However, with respect to preference, there was some apparently conflicting information, with one study noting more patients who had a COL or CTC would recommend the test to a friend in the same medical circumstances than those who had a CCE (96% vs 94% vs 88% respectively, p=0.001), but in another study there were more instances of reasons to prefer CCE than COL (note: it was not clear if the total number of patients who preferred CCE was greater). There were limited data for post-polypectomy surveillance patients, and it is unclear if the findings are generalisable to this population. The impact on patient preference of: the risk of having to have a subsequent COL; the comparative accuracy of the tests; and of different bowel preparation regimens did not appear to be well-investigated.

Cost-effectiveness results

For COL-eligible patients within all three main analysis populations, the EAG's model suggests that CCE is expected to lead to small quality-adjusted life year (QALY) losses and incur higher costs than COL; therefore, CCE is expected to be dominated by COL. The main reasons underpinning this finding are: (i) COL is assumed to have higher sensitivity than CCE for detecting advanced adenomas (AAs) and CRC which leads to slightly fewer QALYs for CCE; (ii) a large proportion of CCEs are incomplete and these patients are assumed to require further tests, which leads to increased costs, and (iii) patients in whom CCE detects significant bowel pathology also require COL/flexible sigmoidoscopy (FSIG) to enable biopsy or polypectomy, which also leads to increased costs. For COL-ineligible patients, CCE is either expected to be dominated by CTC or it has an incremental cost-effectiveness ratio (ICER) which is markedly higher than £30,000 per QALY gained. The main reasons for this finding are: (i) CTC is assumed to have greater sensitivity than CCE for detecting AAs and CRC which leads to slightly

fewer QALYs for CCE in the symptomatic FIT 10-100µg/g and surveillance populations; (ii) the cost per CTC procedure is lower than that for CCE, and (iii) a large proportion of CCEs are incomplete and these patients are assumed to require CTC as a replacement test, leading to increased costs.

Despite these findings, CCE is predicted to lead to substantial reductions in the number of COLs required, particularly for the COL-eligible symptomatic populations. This may help to release capacity in currently constrained endoscopy services.

1.5 Discussion

Strengths and limitations in the clinical evidence base

The strengths of this work are that the systematic review was conducted following a rigorous and high-quality methodology including a comprehensive search strategy, double-screening of all retrieved records, double-checking of all extracted data and a high quality statistical synthesis conducted using a Bayesian approach. There are, however, some significant limitations to the review, mostly relating to the quantity of data available that met the decision problem outlined in the NICE scope. Notable amongst the limitations was the necessity to widen the inclusion criteria because of a lack of relevant data. This resulted in the inclusion of diagnostic test accuracy studies with uncertain generalisability in terms of the populations recruited, and data on prevalence of underlying pathology and capacity spared being derived from studies that did not ascertain FN results amongst those who did not have a positive CCE. The impact and direction of effect of these limitations in the rigour and relevance of the evidence base, and of obtaining test accuracy and prevalence estimates from different sources, are difficult to quantify or predict.

Strengths and limitations relating to the health economic analysis

The EAG's economic model is subject to several strengths. Of particular note: the economic analysis is consistent with the NICE Reference Case and aligns with the final NICE scope; the EAG's model uses data from the NHSE CCE Pilot Study to inform estimates of the prevalence of significant bowel pathology, the CCE completion rate and the use of COL/FSIG as a subsequent luminal investigation; [redacted]; long-term outcomes are informed by the MiMiC-Bowel screening model, and a comprehensive range of sensitivity analyses has been conducted to explore key uncertainties. Limitations of the EAG's model include: inconsistencies in the definitions of polyp risk groups between evidence sources; the need for additional assumptions to derive prevalence estimates from the NHSE CCE Pilot Study; uncertainty in the estimates of diagnostic test accuracy for CCE and comparators, and the exclusion of older or frail patients from the economic analyses.

Implications for service provision

The introduction of CCE in routine NHS practice would require consideration of the following issues:

- Which patients might be suitable for CCE (e.g., based on their underlying level of risk and likely need for subsequent COL)?
- Which healthcare professional(s) should provide pre-assessment for CCE in order to ensure patient safety, reduce the risk of AEs and optimise completion rates?
- Where should the capsule be swallowed (in a hospital, primary care or at home)?
- Which healthcare professional(s) should supervise swallowing of the capsule?
- What measures should be in place to mitigate the risks of capsule retention (e.g., use of dissolvable patency capsules and/or computed tomography [CT] scans)?
- Which healthcare professional(s) should read and interpret the recorded capsule data?
- What measures can be implemented to improve capsule completion rates (e.g., bowel preparation)?

As indicated by the EAG's health economic analysis, the use of CCE is also expected to impact on the provision of other health care services by freeing up capacity for colorectal endoscopy services.

Suggested research priorities

Research priorities include the following:

- Further studies to assess the diagnostic test accuracy of CCE in the populations listed in the NICE scope would be valuable in reducing current uncertainty. It is anticipated that the ongoing ColoCap study (NIHR158034) will provide key evidence in this area.
- Further research into the optimal setting for delivering CCE (e.g., primary care, secondary care or at home) may help to reduce service implementation costs.
- Qualitative research into patient experience may help to identify barriers and facilitators to the acceptability and uptake of CCE.
- Further research into CCE bowel preparation may help to further improve test completion rates and reduce costs.
- An evaluation of artificial intelligence/machine learning alongside CCE may help to understand the impact of such technologies on the diagnostic accuracy of CCE.

2. BACKGROUND AND DEFINITION OF THE DECISION PROBLEM

2.1 Background to the condition

Colorectal cancer (CRC), which is also known as bowel cancer, is a type of cancer that arises in the colon or the rectum. CRC was the fourth most common cancer and the second most common cause of cancer deaths in England in 2017-2019. Approximately 36,500 people in England are diagnosed with CRC each year and around 13,700 people in England die from the disease each year.[1]

2.1.1 Aetiology, pathology and prognosis

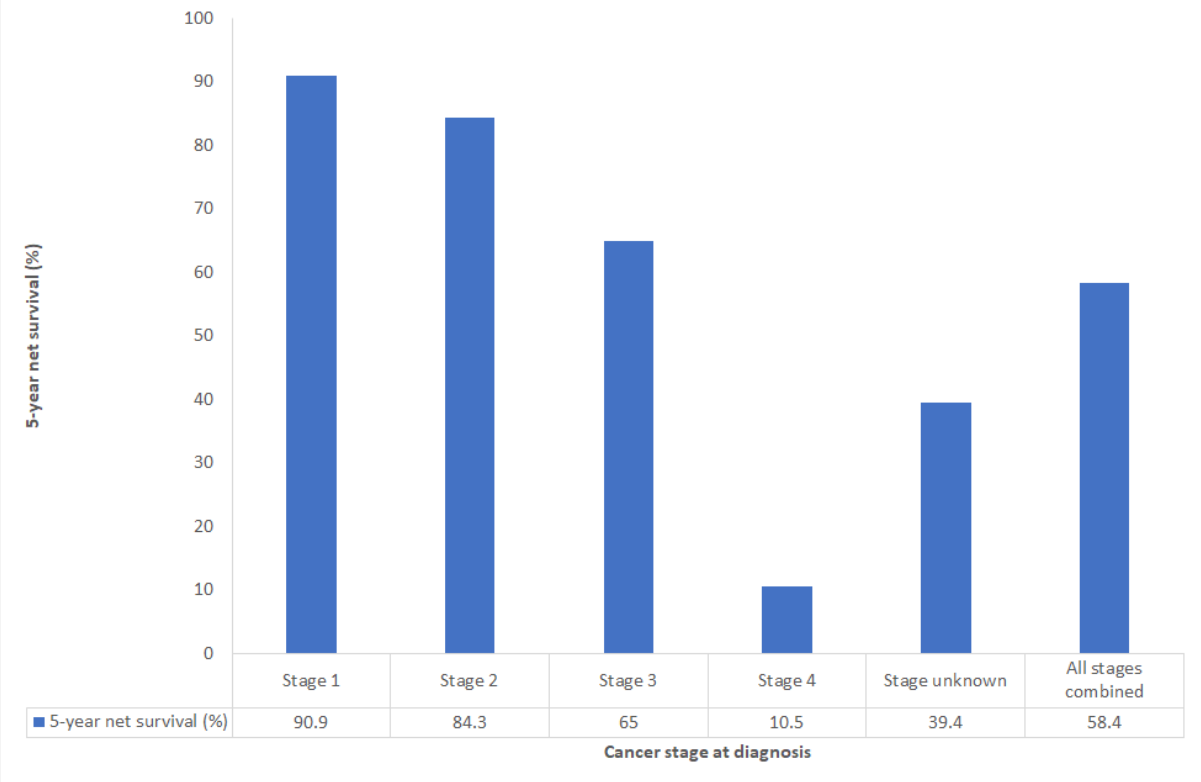
Risk factors for CRC include older age, family history, genetic conditions such as familial adenomatous polyposis (FAP) and Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer [HNPCC]), long-standing inflammatory bowel disease (IBD), and diet and lifestyle factors.[2, 3] Approximately two-thirds of cases of CRC occur in people with no hereditary predisposition, and are caused by a wide range of genetic mutations and epigenetic aberrations that may occur as a result of potentially modifiable risk factors. Around 25% of cases of CRC occur in individuals with a family history of CRC and approximately 5% are attributable to hereditary cancer syndromes (FAP or Lynch syndrome).[4]

Most cases of CRC arise from a prior adenomatous polyp in the bowel,[5] through a process which is known as the adenoma-carcinoma sequence.[6] A polyp is a growth of tissue in the inner lining of the bowel which projects into the lumen of the bowel. Colorectal polyps are very common and can be found in approximately one in four people aged 50 years or older.[7] A person may have one or several polyps and they are slightly more common in men.[8, 9] The exact cause of polyps is not known. The vast majority of polyps do not turn into cancer.[10] Colorectal polyps can be classified according to their macroscopic appearance as sessile (flat or dome-shaped growths which arise directly from the mucosal layer) or pedunculated (mushroom-like growths which extend from the mucosa on a thin stalk). Polyps can also be classified histologically as neoplastic (including adenomas and sessile serrated polyps) or non-neoplastic (including hyperplastic, hamartomatous and inflammatory polyps).[11] Neoplastic adenomas and sessile serrated polyps harbour premalignant potential and may become cancerous. The Paris classification[12] allows for the standardisation of polyp morphology and can be used to predict the likelihood of malignant disease. It has been shown that removing adenomatous polyps disrupts the adenoma-carcinoma sequence and can reduce the risk of developing CRC by up to 90%.[13] The removal of adenomatous polyps has also been shown to lead to a 53% reduction in the risk of mortality.[14]

The prognosis of patients with CRC is dependent on the stage of the tumour at diagnosis. Earlier-stage CRC is curable for the majority of patients. However, later-stage disease is associated with low 5-year

survival rates. Therefore, the earlier detection of CRC is thought to be associated with improved survival. Figure 1 presents data from NHS Digital on 5-year net survival for all persons diagnosed with CRC during the period 2016-2020 and followed up to 2021.[15] Net survival rates are higher for individuals with early-stage CRC (stages 1 and 2) compared with individuals with late-stage disease (stages 3 and 4). Five-year net survival for individuals with stage 4 CRC is particularly low at 10.5%.

Figure 1: 5-year net survival by colorectal cancer stage

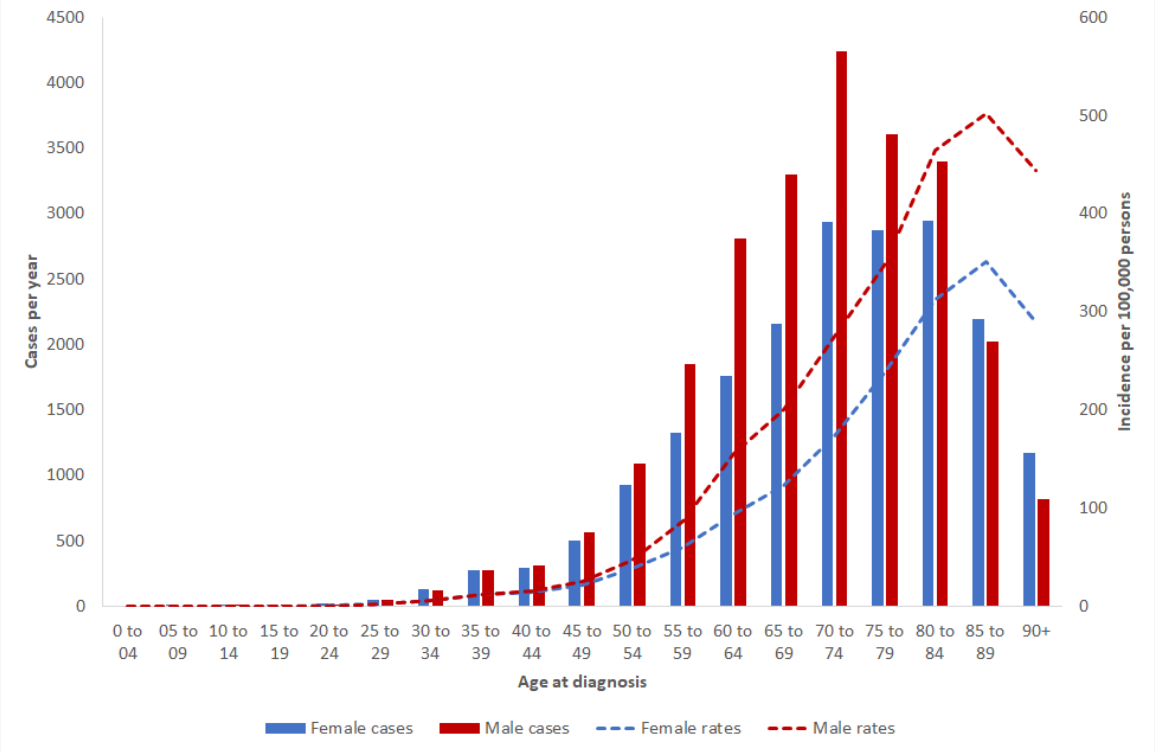


Source: NHS Digital

2.1.2 Epidemiology

Figure 2 presents estimates of CRC incidence by age and sex for the UK, based on data from 2017-2019 published by Cancer Research UK.[1] The incidence of CRC varies by both age and sex. Around 60% of cases occur in individuals aged 70 years and over and the disease is more common in men than women (55% versus 45%).

Figure 2: Colorectal cancer incidence by age and sex, UK, 2017-2019



Source: Cancer Research UK

2.1.3 Burden of disease

CRC is the second most common cause of cancer death in the UK, with an age-standardised mortality rate of 26.7 deaths per 100,000 individuals. The age-standardised mortality rate is higher in men than women (33.2 versus 21.5 deaths per 100,000 individuals). During the period 2017-2019, an average of 13,684 people died from CRC in England each year.[1] The disease and its treatment can have a marked impact on a patient's health-related quality of life (HRQoL). Previous systematic reviews of preference-based utility estimates for alternative CRC states[16, 17] suggest that HRQoL for people with advanced disease is particularly poor, although available estimates vary considerably between studies, with reported utility values ranging from 0.25 to 0.84.[17]

2.1.4 Current methods for staging of CRC

CRC is most commonly staged using the Tumour Node Metastasis (TNM) staging system. The most recent (eighth) edition of the TNM staging classification was published by the American Joint Committee on Cancer (AJCC) in 2017.[18] Under the TNM staging system, T (tumour) describes the size of the tumour, N (node) describes whether the cancer has spread to the lymph nodes and M (metastasis) describes whether the disease has spread to other organs in the body. Less commonly, CRC is staged using the numerical staging classification, the Dukes' staging classification[19] or the modified Astler-Coller version of the Dukes' staging classification.[20] The correspondence between these staging systems is summarised in Table 1.

Table 1: AJCC 8th edition anatomic stage / prognostic groups

Stage	T	N	M	Dukes' stage	Modified Astler-Coller stage
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T3b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

T - tumour; N - node; M - metastasis; Tis - tumour in situ

2.2 Current service provision

2.2.1 FIT testing in screening and primary care

The NHS Bowel Cancer Screening Programme (BCSP) is currently using Faecal Immunochemical Testing (FIT) as a biennial screening test for CRC for people aged 50 to 74 years.[21] The BCSP currently operates a FIT threshold of 120 micrograms of haemoglobin per gram of faeces (120µg/g). Individuals with a positive FIT screening test are invited for further luminal investigations in secondary care, usually using optical colonoscopy (hereafter referred to as "COL"). Patients in whom polyps are found at COL following a positive screening test may be invited to subsequently attend post-polypectomy surveillance (see Section 2.2.4).

People may also present to their General Practitioner (GP) with signs and symptoms suggestive of CRC and may receive a FIT test. National Institute for Health and Care Excellence (NICE) Diagnostics Guidance 30 (DG30)[22] recommended the use of FIT for people with low-risk symptoms that may be suggestive of CRC. In August 2023, DG30 was replaced by DG56,[23] which recommends the use of FIT in primary care using the HM-JACKarc or OC-Sensor FIT tests for adults with certain symptoms and signs of CRC other than rectal or anal mass and anal ulceration. The recommendations account for differing risks of CRC according to the age of the patient and the symptoms which are present. The 2022 British Society of Gastroenterology (BSG) and Association of Coloproctology of Great Britain and Ireland (ACPGBI) guideline on the use of FIT in people with symptoms of CRC[24] also recommends the use of FIT in primary care for all people with clinical features of CRC to prioritise referral for urgent investigation. The current FIT threshold used in a primary care setting is 10µg/g.

Patients may also be referred for further investigations for CRC in secondary care through other routes (e.g., COL surveillance for people with long-standing ulcerative colitis [UC], or via other tests for inherited CRC). These populations are not considered within this assessment.

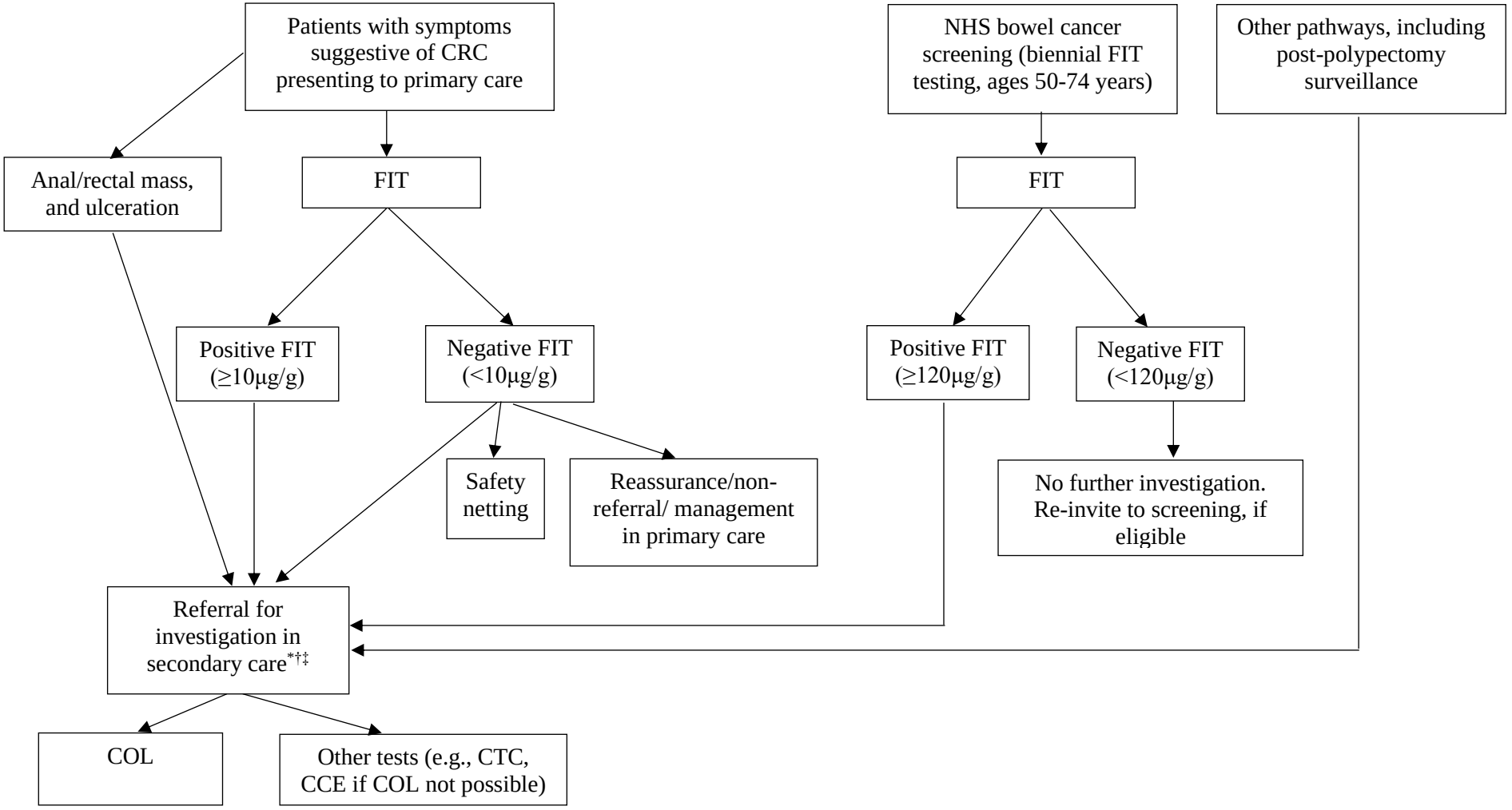
2.2.2 Colorectal cancer referral pathway

The pathways for referral for further investigation of CRC in secondary care are summarised in Figure 3. People who present to primary care with a FIT result of at least 10µg/g are referred under a suspected cancer referral pathway for CRC. People who do not return the faecal sample or who have a FIT result below 10µg/g may still be referred to an appropriate secondary care pathway if there is strong clinical concern of cancer due to ongoing unexplained symptoms. For patients who are not referred to secondary care due to a negative FIT test, safety netting should be in place, which may involve repeat FIT testing, strategies for diagnosing other gastrointestinal (GI) conditions such as IBD, or other monitoring in primary care.

In October 2023, the NHS introduced the Faster Diagnosis Standard (FDS) which aims to ensure that patients with suspected cancer receive a diagnosis or have cancer ruled out within 28 days of referral. The FDS replaced the previous Two Week Wait (2WW) standard. The suspected cancer pathway referral involves an urgent FDS referral directly by the GP after a clinical assessment of symptoms, and the referral would be for the most appropriate test, including COL or computed tomography colonography (CTC), and/or an urgent appointment with a specialist. Patients may also be referred for further investigation in secondary care following a positive FIT screening test or through a variety of other routes, including scheduled surveillance in patients who have previously undergone polypectomy. The 2022 joint ACPGBI/BSG guideline on the use of FIT[24] states that COL is regarded as the gold standard diagnostic investigation for CRC, and CTC is regarded as an equivalent to COL for patients with symptoms suggestive of CRC. For some people who are unable to undergo COL, colon capsule endoscopy (CCE), the intervention under consideration within this assessment, has been used in some centres in England.

COL involves the insertion of a long, thin, flexible tube with a small camera inside into the rectum to directly visualise the rectum and colon (to the caecum). COL may be diagnostic or therapeutic; the former allows only for visualisation of the bowel and for a biopsy to be taken, whereas the latter includes the removal of polyps at the point of detection. CTC, which is also sometimes called computed tomography (CT) colonoscopy or virtual colonoscopy, uses CT scanning to take multiple detailed cross-sectional images of the colon and rectum. Both COL and CTC require bowel preparation prior to the procedure. Some people are unsuitable for or unwilling to undergo COL procedure (e.g., older, frail patients) and people in whom a complete COL is not achieved may require further investigation using an alternative diagnostic test. For these people, CTC is sometimes used. Some people may not be suitable for either COL or CTC and may undergo other less invasive diagnostic procedures (e.g., CT scans).

Figure 3: Current screening and symptomatic referral pathways for CRC



CRC - colorectal cancer; FIT - faecal immunochemical tests; COL - colonoscopy; CTC - computed tomography colonography; CCE - colon capsule endoscopy
**Referral includes an appointment to determine the most appropriate test for the patient. Includes urgent FDS and non-urgent pathways*
†Patients may still be referred despite a negative FIT if there is strong clinical concern of cancer because of ongoing unexplained symptoms
‡CCE is not recommended for use in a screening setting in the UK

2.2.3 Treatment of colorectal adenomas

Colorectal polyps are usually removed at the point of detection via polypectomy which is performed during the COL procedure. Polypectomy can also be performed during flexible sigmoidoscopy (FSIG), which is a similar procedure to COL, but is limited to visualisation of the rectum, sigmoid and up to the splenic flexure. Polypectomy involves removing the polyp from the lining of the bowel wall using biopsy forceps or snare polypectomy. Snare polypectomy can be hot or cold – hot snare polypectomy involves putting a snare around the base of the polyp and burning through the tissue with an electric current (diathermy) whereas cold snare polypectomy does not use diathermy. For larger or complex polyps, advanced endoscopic colorectal polyp removal techniques such as endoscopic mucosal resection (EMR) may be required. EMR involves passing a needle through the colonoscope and inserting it under the polyp and then injecting a fluid to lift the polyp away from the bowel wall to aid polyp removal. Surgery is infrequently required for the removal of colorectal polyps. After polypectomy, histopathology is used to determine the polyp sub-type, degree of dysplasia and completeness of polyp excision. Following polypectomy, patients may be invited to undergo subsequent adenoma surveillance using COL if the baseline COL indicates high-risk findings (see Section 2.2.4).

2.2.4 Post-polypectomy surveillance

The BSG, the ACPGBI and Public Health England (PHE) have jointly published updated post-polypectomy and post-CRC resection surveillance guidelines for people aged 18 years and over.[10] The guideline recommendations for the use of post-polypectomy surveillance are largely dependent on whether high-risk findings are identified at the baseline COL. In this guideline, high-risk findings are defined as: (i) ≥2 premalignant polyps including at least one advanced colorectal polyp (defined as a serrated polyp of at least 10mm in size or containing any grade of dysplasia, or an adenoma of at least 10mm in size containing high-grade dysplasia), or ≥5 premalignant polyps. The guideline recommends that people with high-risk findings at their baseline COL should be offered a one-off surveillance COL three years later, whereas people without high-risk findings are not offered further colonoscopic surveillance, but are instead advised to participate in bowel cancer screening when invited. The guideline also makes recommendations for post-polypectomy surveillance in people with CRC and people with large non-pedunculated colorectal polyps (LNPCPs). The guideline recommends no surveillance if the patient's life expectancy is less than 10 years or if they are older than approximately 75 years of age. Separate guidelines have been published for the management of people with inherited CRC;[25] these guidelines are not discussed here.

2.2.5 Treatment of CRC

NICE Guideline 151 (NG151)[26] provides recommendations on the management of CRC in adults who are aged 18 years and over. Treatment planning takes place in a multidisciplinary team (MDT) setting. Appropriate treatment options for people with diagnosed CRC are dependent on the stage and location

of the tumour, the patient's fitness and their ability to tolerate adverse events (AEs), as well as patient preferences. Surgical resection is the cornerstone of treatment for people with non-metastatic, operable CRC. Adjuvant chemotherapy may also be offered to people with stage III colon cancer who have had their tumour completely resected. Neo-adjuvant/adjuvant radiotherapy or chemoradiation (chemotherapy plus radiotherapy) may be offered to people with non-metastatic rectal cancer. For people with metastatic (stage IV), inoperable CRC, treatment options are focussed on delaying progression and managing symptoms and include immunotherapy, targeted therapy, chemotherapy, palliative radiotherapy and supportive care. A small proportion of patients with operable primary CRC with operable metastatic disease may go on to have surgical treatment with or without neo-adjuvant therapy. For a small proportion of patients with initially inoperable disease, chemotherapy and targeted therapy options can enable downstaging and subsequent surgical resection of initially unresectable metastases in the liver, or less commonly, the lungs.

2.3 Description of the technology under assessment

2.3.1 PillCam COLON 2

CCE is a painless procedure that uses a camera to examine the large bowel. The patient swallows a pill which contains tiny cameras which take pictures of the lining of the bowel to look for colonic polyps and other abnormal bowel pathologies (including CRC, Crohn's disease [CD] and UC). Several CCE technologies are available. This assessment focuses on one particular model of CCE – PillCam™ COLON 2 (Medtronic Ltd.). Other CCE technologies are not included either as interventions or comparators in this assessment.

The PillCam COLON 2 technology is comprised of 3 components: (1) the capsule; (2) the recorder with sensors and (3) desktop software. The capsule is a single-use device which contains two cameras containing light emitting diodes (LEDs) which illuminate the area around the cameras, a battery, and an antenna. The sensors may either take the form of the PillCam COLON 2 sensor belt which is worn around the patient's waist over a single layer of clothing, or the PillCam COLON 2 sensor array, which is placed directly on the patient's body. These devices receive data from the capsule. The PillCam recorder is a data recording device with a built-in real-time viewer, which is attached to the sensor belt or sensor array. Following the procedure, the physician downloads the images from the PillCam recorder to the desktop software for interpretation and analysis. The information provided by the procedure can help clinicians to decide whether further investigations and treatments are necessary.

The PillCam COLON 2 capsule is swallowed under clinical supervision following a bowel cleansing routine which starts the day before the procedure. 'Booster' medicines (typically sodium phosphate and/or an oral iodinated contrast medium) are taken after the capsule has been swallowed which help to propel the capsule through the colon. The capsule captures images over a period of 10 hours or more,

depending on how long the capsule remains in the GI tract. Images are captured at a variable rate ranging from 4 to 35 frames per second; the frame rate changes when the technology detects a change in the image, or when the capsule is in motion. Images are sent from the capsule to the data recorder using radiofrequency. After the capsule is excreted, the raw data are processed using PillCam desktop software and compiled into a video for review. The technology provides functionality to play, rewind and fast-forward the video whilst making anatomical landmarks and thumbnails containing images of interest. After viewing the video and creating the findings, an interpretation of the study can be summarised in a patient report. The video and report must be interpreted by skilled personnel. A dissolvable patency capsule may need to be used prior to the CCE procedure in some patients where there is risk of retaining the capsule within the small bowel.

2.3.2 Current recommendations on the use of CCE for the identification of colorectal polyps or CRC

Several clinical guidelines mention the use of CCE for the investigation of symptoms suggestive of CRC or for use in a screening setting:

- The 2012 European Society of Gastrointestinal Endoscopy (ESGE) guideline on CCE[27] provides recommendations for the implementation of CCE in a clinical setting with the intention of standardising reporting and post-CCE work-up. The guideline states that CCE is feasible and safe and appears to be accurate when used in average-risk individuals, but highlights a lack of studies in a screening setting.
- The 2020 ESGE and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) updated guideline on the use of imaging alternatives to COL[28] suggests the use of CCE for faecal occult blood test (FOBT) or FIT test-positive cases with incomplete or unfeasible COL, and for patients with non-alarm symptoms in whom COL is contraindicated or not possible. In centres with expertise in and availability of CCE, CCE may be considered on the same day or the next day if COL is incomplete.[28] The guideline does not recommend the use of CCE as a primary screening tool for CRC.
- The 2020 European Society for Medical Oncology (ESMO) clinical practice guideline for the diagnosis, treatment and follow-up of localised colon cancer does not recommend the use of CCE as a primary screening tool for CRC[29] The use of CCE in other clinical settings is not discussed within the guideline.
- The 2020 joint BSG/ACPGBI/PHE guideline for post-polypectomy and post-colorectal cancer resection does not recommend the use of CCE for surveillance after resection of premalignant colorectal polyps because of a lack of evidence.[10]

A review by the BSG[30] suggests that it is likely that CCE would be best suited for use in low-risk patients (those with a FIT score of <10µg/g) to investigate symptoms where subsequent COL is much less likely to be needed.

2.3.3 Current usage of CCE in the NHS

Currently, CCE is not commonly used as a diagnostic tool for the detection of colorectal polyps or CRC in the NHS, except when other tests are not possible. To date, CCE has been used in practice in a minority of NHS centres. Other types of video capsule endoscopy are however used in the NHS in non-cancer pathways to assess GI symptoms, for example, for the diagnosis of IBD and coeliac disease and to investigate unexplained GI bleeding. These alternative technologies and populations are outside of the remit of this appraisal.

2.3.4 UK CCE pilot studies

Four pilot studies of CCE have been undertaken in the UK:

(i) The ScotCap study which was undertaken in NHS Grampian, NHS Highland and NHS Western Isles.[31] Within this study, a CCE service was trialled as an alternative to direct COL referral and was used to triage surveillance patients and symptomatic patients with a positive FIT.

(ii) The NHSE CCE Pilot Study which was undertaken in 55 sites across England.[32] The study included both symptomatic patients and post-polypectomy surveillance patients.

(iii) A small single-centre pilot study conducted in Barnsley, England.[33] Within this study, CCE was offered to people with symptoms and a positive FIT.

(iv) A small pilot study which was conducted in four health boards in Wales.[34] This study included patients with persistent symptoms and a negative FIT (low-risk).

Available data from these pilot studies are reported in Section 3.3.3 of this report. Currently, a CCE service is available in a limited number of health boards in Scotland. CCE has not yet been embedded in national clinical pathways in either England or Wales.

2.4 Description of the decision problem

This assessment aims to evaluate whether CCE for detecting colorectal polyps and CRC represents a clinically effective and cost-effective use of NHS resources. Within this assessment, we will explore the potential cost impacts associated with supervised swallowing of the PillCam COLON 2 capsule in both secondary care and community settings.

2.4.1 Populations and relevant subgroups

Based on the final NICE scope,[35] this assessment focuses on the following main populations:

- Adults with lower GI signs or symptoms suggestive of CRC who are referred to secondary care. Where evidence is available, subgroups for this population include:

    - People with a positive FIT score of 10-100µg/g
    - People with a negative FIT result of <10µg/g with concerning clinical symptoms
- Adults who are due to have a post-polypectomy surveillance COL at 3 years because of high-risk findings at their baseline COL.

Where evidence is available, subgroups may include:

- People who have declined COL
- People who have had an incomplete COL despite adequate bowel preparation.

Clinical experts have advised NICE that CCE is not appropriate for use in people with a rectal or anal mass or anal ulceration; therefore, these populations have been excluded from this assessment.

2.4.2 Place of the intervention in the treatment pathway

The 2020 ESGE/ESGAR updated guideline on the use of imaging alternatives to COL suggests the use of CCE for FOBT or FIT positive cases with incomplete or unfeasible COL, and for patients with non-alarm symptoms in whom COL is contraindicated or not possible.[28] As noted in Section 2.3.3, CCE has been used as a colonic imaging modality for certain patients in some centres in England. The focus of this assessment is on the use of PillCam COLON 2. The technology may provide an alternative to COL or CTC to rule out polyps or CRC or may be used as a filter or triage test prior to COL.

Waiting times from referral to undergoing COL are long for certain groups of patients. The National Endoscopy Database (NED) records data on endoscopy use in the NHS with the aim of addressing unwanted variation in endoscopy performance through the provision of access to detailed performance analytics and reports.[36] A total of 867,381 COL procedures were recorded on the NED in 2023. Data published by the National Health Service England (NHSE) in October 2024 on cancer waiting times for patients with lower GI cancer or suspected lower GI cancer referred on an urgent cancer pathway indicate that around 63% of patients were diagnosed with cancer or had cancer ruled out within 28 days.[37] This is lower than the target of 75%. Clinical advice received by the EAG suggests that the longest waiting times are for those patients with a FIT score of ≤10µg/g who are referred for COL due to concerning clinical symptoms. The EAG's clinical advisors stated that these patients typically wait 30-40 weeks before being seen in clinic, although these waiting times will vary between centres. It is anticipated that CCE may relieve some of these pressures on endoscopy services by reducing referrals for COL in patients who are less likely to require further luminal investigation.

As discussed in Section 2.3.2, CCE has been considered for use as a primary screening tool for people without symptoms, but the technology has not been recommended in this setting in clinical guidelines.[29, 38] The use of PillCam COLON 2 in this setting is not considered within this assessment.

2.4.3 Relevant comparators

There are two comparators for CCE which are considered within this assessment: COL and CTC. For patients in whom COL is not suitable, CTC is the only comparator.

2.4.4 Outcomes

The following outcomes are considered in this assessment, as described in the final NICE scope:[35]

Intermediate measures:

- Diagnostic accuracy for detecting polyps (per patient and per lesion)
    - Measuring less than 6mm
    - Measuring between 6 and 9mm
    - Measuring 10mm or more
- Diagnostic accuracy for detecting:
    - CRC
    - Other bowel pathology including IBD
- CCE completion rates (including excretion of the capsule within its battery life with complete visualisation of the colon)
- Bowel cleansing level (adequate vs. inadequate)
- Detection rates with CCE, COL or CTC for: polyps (including adenomas); CRC; other bowel pathology
- Uptake
- Reduction in the number of COLs/number of COLs potentially prevented (diagnostic, therapeutic, urgent and non-urgent)
- Proportion of people requiring follow-up COL or other investigations such as FSIG after CCE/COL and CTC (diagnostic, therapeutic, urgent, non-urgent)
- Number of polyps missed (including high-risk, intermediate-risk and low-risk polyps)
- Numbers of cancers missed.

Clinical outcomes:

- Number of CRC diagnoses
- Stage of detected cancers
- Number/proportion of people identified with other bowel pathologies
- Number/proportion of people with advanced adenomas (AAs) detected or detected and treated
- Morbidity including AEs associated with CCE, COL and CTC

- Mortality.

Patient-reported outcomes:

- HRQoL
- Anxiety associated with waiting for procedures or test results because of diagnostic delays, and further diagnostic work-up
- Preference for CCE versus COL or CTC.

Health economic outcomes:

Costs are considered from an NHS and Personal Social Services (PSS) perspective. The cost-effectiveness of CCE versus relevant comparators is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Costs for consideration include:

- Costs of the device (including consumables, software, maintenance, service costs and patency capsules)
- Cost of staff (including pre-assessments, supervision of swallowing, reading and reporting time) and associated training
- Costs of follow up testing and care including COL
- Costs associated with CCE and other investigations
- Implementation costs
- Costs of treating cancer
- Medical costs of AEs from the procedure or further diagnostic work-up, including those associated with false test results and inappropriate investigations.

2.5 Aims and objectives of the assessment

The main research question to be addressed is: *"Does the use of colon capsule endoscopy in adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer, or those due to have post-polypectomy surveillance 3 years after their index colonoscopy represent a clinically and cost-effective use of NHS resources, taking into consideration potential colonoscopy capacity constraints?"*

The objectives of the assessment are as follows:

- To conduct a systematic review of the published evidence on the effectiveness and cost-effectiveness of PillCam COLON 2 for detecting colorectal polyps and CRC
- To develop a health economic model to assess the cost-effectiveness of PillCam COLON 2 compared with COL and CTC from the perspective of the NHS and PSS.

3 CLINICAL EFFECTIVENESS

3.1 Methods

A systematic review was conducted to identify evidence on the clinical effectiveness, diagnostic accuracy, patient preferences and safety of CCE using PillCam COLON 2. The methods for the review have been previously published in the EAG's protocol for the appraisal[39] (available from https://www.nice.org.uk/), and the review protocol is registered on PROSPERO (registration number CRD42024586405).

3.1.1 PICOS inclusion criteria

The inclusion criteria for the review were aligned with the decision problem defined in the final NICE scope.[35] These criteria are detailed in Sections 3.1.1.1 to 3.1.1.6 and studies were initially included if they met these criteria. However, insufficient evidence was found that met the original inclusion criteria, and some criteria were widened to allow for the inclusion of the most relevant evidence. A staged approach to widening the criteria was undertaken; this is described in Section 3.2 and in Appendix 1, and protocol changes are noted throughout Sections 3.1.1.1 to 3.1.1.6. Evidence was judged to be insufficient where either no data were identified, or where available data had significant limitations e.g., relating to the outcomes reported, methodologically, in terms of size, or in terms of external validity.

3.1.1.1 Population and subgroups

- Adults with lower GI signs or symptoms suggestive of CRC who were referred to secondary care.
- Adults who were due to have a post-polypectomy surveillance COL at 3 years because of high-risk findings at their baseline COL.

Where evidence was available, subgroups included:

- People with signs or symptoms suggestive of CRC with a FIT score of 10-100µg/g.
- People with signs or symptoms suggestive of CRC with a negative FIT result of <10µg/g with concerning clinical symptoms.
- People who had declined COL.
- People who had an incomplete COL despite adequate bowel preparation.

Studies with wider populations, but which presented data separately for the population(s) or subgroup(s) of interest, were eligible for inclusion.

Changes to protocol: The EAG's protocol stated that where insufficient studies related exclusively to the populations of interest were found, studies would be included with populations comprising more than 80% of participants representing the populations of interest. However, even with this widening of

the criteria, insufficient evidence relating to diagnostic test accuracy in the populations of interest were identified, and the inclusion criteria were widened further, as described in Section 3.2 and in Appendix 1.

Acceptability, uptake and patient preferences for CCE might vary according to socioeconomic and demographic factors such as ethnicity. If available, data would have been extracted and reported separately for such subgroups, but none were identified.

3.1.1.2 Interventions

One intervention was included in the review: PillCam COLON 2 (Medtronic Ltd.).

3.1.1.3 Comparator/reference standard

Data for comparator technologies (COL and CTC) were not systematically reviewed but were included in the model. Data were sought in line with other modelling parameters (see Section 4.3).

For diagnostic accuracy studies, COL was considered the gold standard and the preferred reference standard. Other reference standards could be considered on a case-by-case basis where data using the preferred reference standard were unavailable.

3.1.1.4 Outcomes

Relevant outcomes included the following:

Intermediate measures:

- Diagnostic accuracy for detecting polyps (per patient and per lesion):
    - Measuring less than 6mm.
    - Measuring between 6 and 9mm.
    - Measuring 10mm or more.
- Diagnostic accuracy for detecting:
    - CRC
    - Other bowel pathology, including IBD.
- Capsule completion rates (including excretion of the capsule within its battery life with complete visualisation of the colon).
- Bowel cleansing level (adequate vs. inadequate).
- Detection rates with CCE, COL, or CTC for polyps (including adenomas), cancer, and other bowel pathologies.
- Uptake.

- Reduction in the number of COLs/COLs potentially prevented (diagnostic, therapeutic, urgent, and non-urgent).
- Proportion of people requiring follow-up COL or other investigations such as FSIG after CCE/COL and CTC (diagnostic, therapeutic, urgent, and non-urgent).
- Number of polyps missed (including high-risk, intermediate-risk, and low-risk polyps).
- Numbers of cancers missed.

Clinical outcomes:

- Number of CRC diagnoses.
- Stage of detected cancers.
- Number/proportion of people identified with other bowel pathologies.
- Number/proportion of people with AAs detected or detected and treated.
- Morbidity, including AEs associated with CCE, COL, and CTC.
- Mortality.

Patient-reported outcomes:

- HRQoL.
- Anxiety associated with waiting for procedures or test results because of diagnostic delays and further diagnostic work-up.
- Preference for CCE versus COL or CTC.

Studies were only included if they reported either diagnostic test accuracy (or, upon widening the review criteria, diagnostic yield), patient preference or HRQoL. Other outcomes such as test uptake, bowel cleansing, completion rates and AEs were extracted from these studies only, as a comprehensive review of all these outcomes would have led to large numbers of included studies.

No published evidence for the use of CCE on some of these outcomes was anticipated (e.g., stage of detected cancer, number with AAs), and some outcomes were unavailable from the NHSE CCE Pilot Study.[32] In such instances, outcomes were estimated by the economic model based on other evidence and assumptions (see Section 4.3).

Data relating to small bowel pathologies were not routinely extracted because most studies did not report these data, and the economic model did not include them. Data relating to IBD, diverticulosis or other colorectal diseases were extracted where reported.

The term "detection rate," which appears in the NICE scope,[35] is used quite variably within the literature. In some definitions this is synonymous with the sensitivity of the test, i.e., true-positives

(TPs) divided by all patients with the disease (TPs plus false-negatives [FNs]). This metric generally requires all patients to have received a definitive diagnosis using a reliable reference standard, in order to identify FNs. "Diagnostic yield" is also used within the literature, and this tends to relate to either: (a) the number of patients identified by the test as having the disease (i.e., TPs plus false-positives [FPs]), or (b) the number of patients identified by the test as having the disease, and confirmed by a definitive test as having the disease (i.e., only TPs). In this report, we use the term diagnostic yield in both instances (a) and (b), but when not referring to both, we provide clarity on which type is being reported (see Section 3.3.3.1 and 3.3.3.2).

Changes to protocol: Due to insufficient evidence, or limitations of the included studies, the outcomes criteria were widened to include diagnostic yield studies in some cases, as described in Section 3.2 and Appendix 1. The EAG's clinical advisors and NICE specialist committee members were interested in data on whether CCE "completed" an incomplete COL, i.e., whether the CCE reached the most proximal site of the incomplete COL, as they considered that this was a way in which CCE could be used in clinical practice. In an amendment to the protocol, data were extracted relating to this outcome for studies in patients with incomplete COL.

3.1.1.5 Types of clinical evidence required and study designs

For the review of clinical effectiveness, randomised controlled trials (RCTs) were initially sought, and non-RCTs could be included if no RCTs were available.

Diagnostic test accuracy studies were also eligible for inclusion. For the review of diagnostic test accuracy, only cohort studies that recruited patients regardless of diagnosis were included (i.e., studies that avoided a case-control design). Studies were initially restricted to full-text, English-language articles. Where insufficient data were available, published abstracts were considered for inclusion if they provided relevant outcome data and sufficient methodological details to allow critical appraisal of study quality.

Changes to protocol: Due to insufficient evidence, or limitations of the included studies, the study design criteria were widened to include diagnostic yield studies in some cases, as described in Section 3.2 and Appendix 1. Grey literature sources were not specifically sought, but in a change to the protocol, where they were identified and were relevant, they were included. The NHSE CCE Pilot Study was included in the review using data provided by personal communication with the NHSE Pilot Study Investigators.[40]

3.1.1.6 Exclusion criteria

The following exclusions were applied:

Population:

- Children (aged <18 years old).
- Asymptomatic patients (referred from the BCSP e.g., with a positive FIT).
- People with a rectal or anal mass or anal ulceration.

Intervention:

- PillCam COLON 1 (the earlier version of the technology of interest).
- Other CCE devices.

3.1.2 Search strategy

A comprehensive literature search was undertaken to identify published and unpublished evidence of the diagnostic accuracy of PillCam COLON 2. Following the Cochrane guidance[41] on reviews of diagnostic test accuracy, searches were not restricted to a particular study design and were instead structured around the parts of the bowel and the intervention itself (including alternative names for the device).

Searches were limited to evidence published since 2009 (the year prior to the launch of PillCam COLON 2) and covered the following sources:

- MEDLINE, MEDLINE in Process and Epub ahead of print (via Ovid)
- EMBASE (via Ovid)
- Cochrane Database of Systematic Reviews (via Wiley)
- Cochrane Central Register of Controlled Trials (via Wiley)
- World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP)
- Clinicaltrials.gov.

In order to keep the number of search results manageable, conference abstracts were excluded from the main EMBASE search. Instead, a targeted search was conducted to find relevant abstracts from the following conference series, selected on the advice of clinical experts, from 2014-present:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- European Cancer Summit
- Digestive Diseases Week (DDW)
- United European Gastroenterology Week (UEGW)
- Asian Pacific Digestive Week (APDW)
- British Society of Gastroenterology Annual Meeting (also known as BSG Live).

Searches for published literature were completed on the 9th August 2024. The subsequent search for conference abstracts was undertaken on the 13th August 2024. Full search strategies are reproduced in Appendix 2. Reference lists of existing systematic reviews were checked for additional studies. Through checking reference lists of included studies, a relevant primary study (by Morgan *et al*)[42] was identified that had not been retrieved by the literature search due to its use of the term "capsule colonoscopy" rather than "capsule endoscopy". To ensure that no other relevant studies had been missed for the same reason, we conducted targeted searches of MEDLINE, EMBASE and Cochrane on 24th October 2024. The search identified a total of 84 new results, including Morgan *et al*.[42] On screening, it was observed that most of these were studies of patients taking capsules before other types of COL. No new studies eligible for inclusion were identified through this supplementary search.

Where studies were unclear regarding some details, e.g., recruitment criteria, authors were contacted if the study was of high relevance or of high quality, but authors of studies lower down in the prioritisation of evidence (see Appendix 1) were not contacted due to time constraints.

3.1.3 Study selection

Titles and abstracts retrieved by the search strategy were assessed against the inclusion criteria by two independent reviewers, and irrelevant records were excluded. One reviewer (Reviewer 1) screened records in alphabetical order (by first author surname) in Endnote, whilst another (Reviewer 2) screened records using Endnote and an artificial intelligence (AI) prioritisation algorithm held by the University of Sheffield Computer Science department. The use of the AI prioritisation formed part of a Study Within a Review (SWAR) to be published subsequently. All records were screened by both reviewers. Records included by Reviewer 2, but not by Reviewer 1, were reviewed by Reviewer 1 to ensure that no studies had been missed by Reviewer 1. Any continuing disagreement was resolved through discussion. Full-texts of records included based on their titles or abstracts were obtained and assessed against the inclusion criteria by one reviewer and inclusion was confirmed by a second reviewer. Input from the EAG's clinical advisors and the project lead was also obtained when necessary.

3.1.4 Data extraction

For diagnostic test accuracy studies, a data extraction form was constructed in Microsoft Excel, piloted, and adapted where necessary. For other study designs, data were extracted into report-ready tables in Microsoft Word which focused on the data fields of most importance to the interpretation of the data. A list of data extraction fields is provided in Appendix 3, Table 55, for the diagnostic test accuracy studies. For the other reviews, the data extraction fields are as reported in the tables presented.

Data extraction was performed by one reviewer and checked by a second reviewer. Discrepancies were resolved through discussion or consultation with the clinical advisors. Data from multiple publications of the same study were consolidated into a single dataset. Where studies included comparators or

subgroups outside the scope of the review, only relevant data were extracted. Relevant systematic reviews identified during study selection and scoping were initially used for data extraction, where appropriate. In such instances, the data were checked against the original journal article and any discrepancies were checked by a second reviewer.

3.1.5 Risk of bias assessment

For the review of diagnostic test accuracy, the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool[43] was applied to assess risk of bias and applicability. The QUADAS-2 tool comprises four domains: patient selection; index test; reference standard; and flow and timing. Each domain has signalling questions that are scored "yes", "no" or "unclear", and an overall risk of bias ("high", "low" or "unclear") is scored for the domain based on the lowest score ("yes" highest, "unclear" intermediate, "no" lowest) given to the signalling questions. Applicability (or generalisability) of the study to the review question is judged based on one single question for each of three domains: patient selection; index test and reference standard. The tool was adapted to the specifics of the review question, in accordance with "Phase 2: Review-specific tailoring" outlined by the tool developers in Whiting *et al.*, 2011,[43] and the criteria are presented in Appendix 4. This tailoring was to provide guidance on how to answer the signalling questions, e.g., by specifying the time within which the reference standard should be conducted. No questions were omitted from the tool.

For patient preference studies, the Mixed Methods Appraisal Tool (MMAT) tool[44] was used. The MMAT is designed to assess five different study types: qualitative; quantitative - randomised controlled studies; quantitative - non-randomised controlled studies; quantitative - observational descriptive studies, and mixed methods. Each study was appraised according to the criteria specific to its methodological design, with each criterion rated as "yes," "no," or "unclear." For mixed methods studies, the appraisal incorporated the qualitative criteria, the relevant quantitative criteria, and the mixed methods criteria.

Studies were quality-assessed by one reviewer, with results checked by a second reviewer. Discrepancies were resolved through discussion, involvement of a third reviewer, or consultation with a clinical advisor.

Sensitivity analyses assessing the impact of study quality on the evidence base were planned if there were sufficient data. However, insufficient evidence and high levels of heterogeneity in other study characteristics prevented a meaningful assessment.

Diagnostic yield studies were not assessed for risk of bias due to their low overall quality when answering questions relating to diagnostic test accuracy.

3.1.6 Methods of analysis/synthesis

For studies of all designs, narrative syntheses were conducted for study and patient characteristics and for outcomes. The narrative syntheses aimed to highlight similarities and differences between the studies, and to highlight any patterns or points of interest in the data.

For patient preference studies, a narrative synthesis of the quantitative and qualitative data was undertaken. The results of both the quantitative and qualitative data were grouped under 5 headings: satisfaction, dissatisfaction, comfort/discomfort, overall preference and other outcomes. These headings were used in Ismail *et al*.[45] to report data, and were selected by the EAG as suitable categories to base a synthesis around because they covered key aspects of patient preference, and were broad enough to encompass data from all four studies included.

For diagnostic test accuracy outcomes with two or more included studies meta-analysis was planned. Meta-analysis was undertaken to estimate the diagnostic accuracy of CCE for ≥6mm polyps, ≥10mm polyps and polyps of any size. Sensitivity analyses were undertaken to exclude studies judged by the EAG to be clinically heterogeneous to other studies, and to test the use of different prior distributions. In the first sensitivity analysis, one study (Omori *et al.* 2024[46]) was excluded from the base case meta-analysis of four studies because it had different inclusion criteria than the other studies, including patients with known upper GI tumours. The second sensitivity analysis explored the use of a non-informative prior distribution for the between-study variation.

The diagnostic data were analysed using a bivariate random effects meta-analysis model.[41] The log odds of sensitivities and specificities were modelled using a bivariate normal distribution which allows for within-study correlation. The random effects model took into account heterogeneity between studies which is generally expected in studies of diagnostic test accuracy. A detailed description of the statistical models used along with the specifications for prior distributions can be found in Section 3.1.6.1.

All analyses were conducted using Markov chain Monte Carlo (MCMC) simulations and were implemented in the R software environment using JAGs and the *rjags* software package.[47] Convergence to the target posterior distributions was assessed using the Gelman-Rubin convergence statistic.[48] Each model was run until convergence was satisfactory and then model parameters were estimated based on a reasonable number of burn-in iterations and thinning.

Results were presented as coupled forest plots and summary receiver operating characteristic (SROC) plots. Estimates of sensitivity and specificity with 95% credible intervals (CrIs, also known as Bayesian confidence intervals [CIs]) were plotted to illustrate the variation among the synthesised studies. A 95%

prediction interval (PrI) was reported to indicate the between-study heterogeneity and a range of values that might be expected in a future study.

3.1.6.1 Statistical models for the meta-analysis

A bivariate random effects meta-analysis model analyses sensitivity and specificity jointly by taking into account the correlation between them. The observed number of true-positives in study i, TP_i, is assumed to be binomially distributed with parameter π_{Ai} representing the study-specific sensitivity given the total number of positives on the reference test such that,

$$TP_i \sim Binomial\left((TP_i + FN_i), \pi_{Ai}\right).$$

Similarly, the observed number of true-negatives in study i, TN_i, is assumed to be binomially distributed with parameter π_{Bi} representing the study-specific specificity given the total number of negatives on the reference test such that,

$$TN_i \sim Binomial\left((TN_i + FP_i), \pi_{Bi}\right).$$

As the study-specific sensitivity and specificity (π_{Ai}, π_{Bi}) are probabilities with values between 0 and 1, we transform them to a real line scale (μ_{Ai}, μ_{Bi}) using the logit (log-odds) function,

$$\mu_{Ai} = \text{logit}(\pi_{Ai}) = \log\left(\frac{\pi_{Ai}}{1 - \pi_{Ai}}\right)$$

$$\mu_{Bi} = \text{logit}(\pi_{Bi}) = \log\left(\frac{\pi_{Bi}}{1 - \pi_{Bi}}\right).$$

Across studies, we model the transformed sensitivity and specificity (μ_{Ai}, μ_{Bi}) and their correlations using a bivariate normal distribution. As heterogeneity is often expected for sensitivity and specificity,[41, 49] we model the transformed probabilities (μ_{Ai}, μ_{Bi}) using a random effects model, i.e., we model (μ_{Ai}, μ_{Bi}) using a bivariate normal distribution with the following specification:

$$\begin{pmatrix}\mu_{Ai} \\ \mu_{Bi}\end{pmatrix} \sim N\begin{pmatrix}m_A \\ m_B\end{pmatrix}, \Sigma_{AB}\Big)$$

$$\Sigma_{AB} = \begin{pmatrix}\sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2\end{pmatrix}$$

where m_A and m_B represent the population mean for logit sensitivity and specificity; σ_A^2 represents the variability in the logit sensitivity between studies, σ_B^2 represents the variability in the logit specificity between studies and σ_{AB} represents the covariance of the logit sensitivity and logit specificity. We rewrite the covariance as $\sigma_{AB} = \rho\sigma_A\sigma_B$, with ρ being the correlation coefficient between logit sensitivity and specificity, σ_A being the between-study SD for logit sensitivity and σ_B being the

between-study SD for logit specificity. Between-study SD is used to quantify the degree of heterogeneity between studies with larger values indicating greater heterogeneity.

Prior distributions are required for the hyperparameters. A vague logistic distribution $Logistic(0,1)$ was used as the prior for the mean parameters m_A, m_B. A uniform distribution $U(-1,0)$ was used as a prior over the correlation coefficient ρ as sensitivity and specificity are often expected to be negatively correlated. Due to the limited number of studies identified, a weakly informative prior distribution - a half normal distribution $HN(0,1)$ - was used as the prior for the SD of the random effects σ_A, σ_B in the base case.[49] Additionally, we also used a vague uniform distribution $U(0,5)$ as the prior for the SD of σ_A, σ_B in sensitivity analysis 2. A total of 1,000,000 iterations with a burn-in of 100,000 and thinning of 10 were used to estimate the model parameters in all analyses.

3.1.7 Methods for estimating health-related quality of life

HRQoL estimates reported in the clinical literature relating to the use of CCE, COL, and CTC were sought amongst studies included in the systematic review. Additional HRQoL data required for the EAG's economic model are described in Section 4.3.

3.2 Changes to the review protocol

3.2.1 Changes to the inclusion criteria

Because insufficient evidence was found that met the initial inclusion criteria, a staged approach to widening the criteria was undertaken. At the title and abstract stage, studies were retained if they were on PillCam COLON 2, were not undertaken exclusively in a screening population and reported either test accuracy, detection rate, diagnostic yield or patient preference. A map of these studies was then constructed with reference to the full-text articles, and criteria were developed in response to the available evidence. In refining the criteria, consideration was given to rigour (methodological quality), relevance (generalisability, i.e., how close the patients recruited were to the population of interest) and the requirements of the EAG's economic model. This resulted in different criteria for different aspects of the review questions, as detailed in Table 2. The process of redefining criteria is detailed in Appendix 1.

Table 2: Criteria that were widened in comparison to the original criteria listed in Sections 3.1.1.1 to 3.1.1.6

Criterion	Original criterion	Widened criterion
Widened 1: Widen population to include test accuracy studies in mixed populations		
Population	>80% patients representing the populations of interest defined in NICE's scope[35]	At least some patients representing the populations of interest defined in NICE's scope[35]
Widened 2: Widen reference standard/outcome to include diagnostic yield studies in scope-defined populations[35] (symptomatic patients) or at least some surveillance populations		
Reference standard	COL or alternatives considered if none using COL	Only some patients received a reference standard
Outcomes	Diagnostic test accuracy	Diagnostic yield
Widened 3: Widen both population and reference standard/outcome to include diagnostic yield studies in patients with incomplete COL or who refused COL, at least 50% of whom were scope-defined populations		
Population	>80% patients representing the populations of interest defined in NICE's scope[35]	>50% patients with incomplete COL or who refused COL, as defined in NICE's scope[35]
Reference standard	COL or alternatives considered if none using COL	Only some patients received a reference standard
Outcomes	Diagnostic test accuracy	Diagnostic yield
Widened 4: For studies in surveillance populations, widen population to include patient preference studies with >50% patients in scope, including some patients under surveillance		
Population	>80% patients representing the populations of interest defined in NICE's scope[35]	>50% surveillance patients defined in NICE's scope[35]

NICE - National Institute for Health and Care Excellence; COL - colonoscopy

3.3 Results

3.3.1 Study selection and prioritisation of evidence

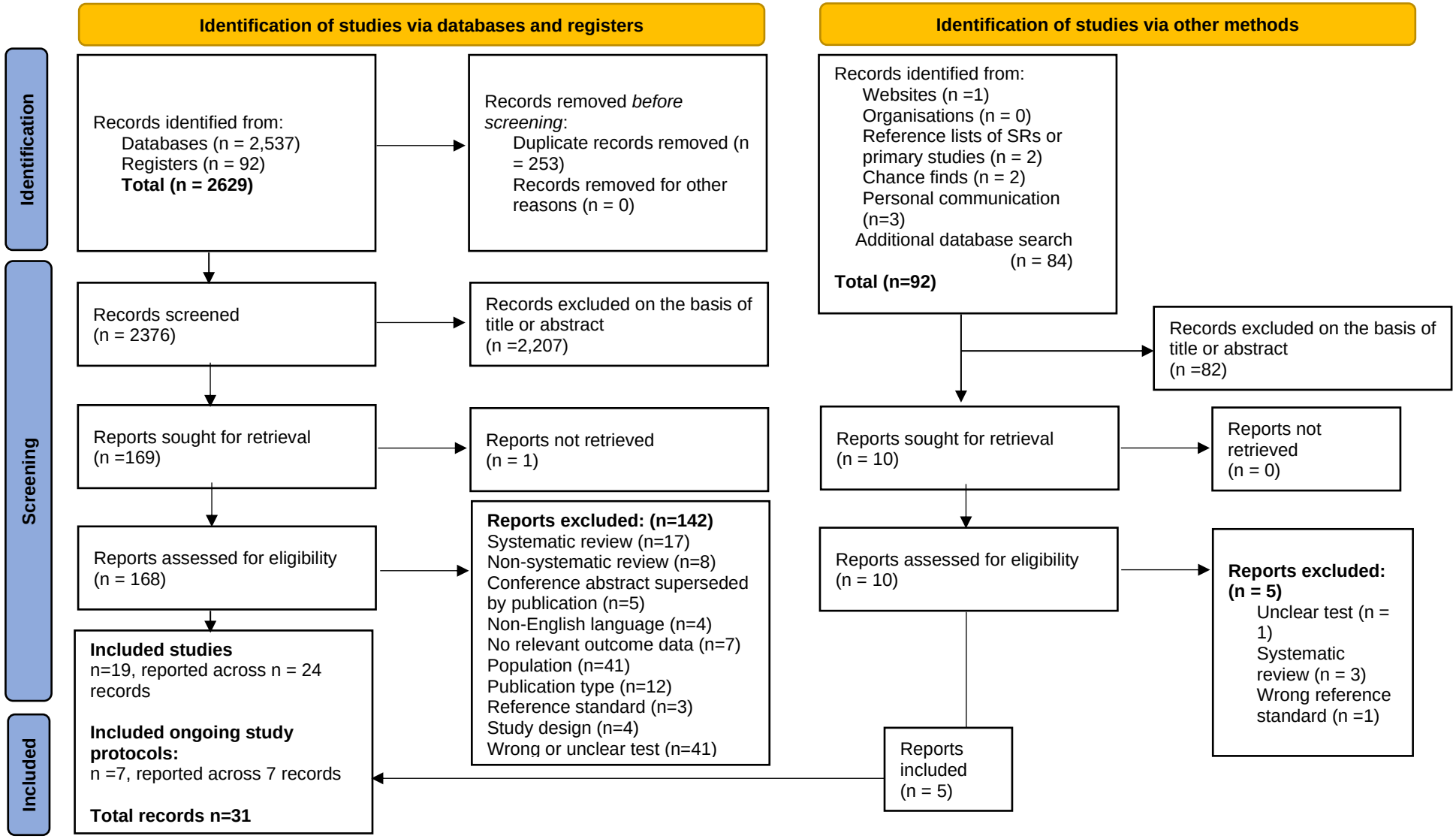
A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[50] flow diagram describing the study selection process is provided in Figure 4. The database searches retrieved 2,376 unique records, and identification of studies from other sources identified 92 records which were considered for inclusion. Of these, 2,289 were excluded on the basis of their title and/or abstract, and the full-texts of 179 studies were sought. Of these, one was unobtainable,[51] and 37[31-34, 40, 42, 45, 46, 52-80] were included in the mapping exercise. After refinement of the inclusion criteria to select the most relevant and/or high-quality studies (see Appendix 1), a total of 147 records were excluded (see Figure 4 and Appendix 5 for reasons), and five groups of studies were identified and included in the review as follows (note - "Widened…" relates to the categories detailed in Table 2):

- Section 3.3.2.1: Diagnostic test accuracy studies meeting the inclusion criteria (n=1)[57]
- Section 3.3.2.2: Diagnostic test accuracy studies in mixed populations (Widened 1, n=5)[42, 46, 60, 75, 77]
- Section 3.3.3.1: Diagnostic yield studies in symptomatic and surveillance populations defined in the scope (Widened 2, n=4, reported across 7 sources)[31-34, 40, 68, 78]

- Section 3.3.3.2: Diagnostic yield studies in patients with incomplete COL or who refused COL (Widened 3, n=7)[53, 56, 58, 62, 72, 73, 76]
- Section 3.3.4: Patient preference studies in the correct population or with >50% correct population some of whom were under surveillance for previous polyps (No widening, n=3, Widened 4, n=1, reported across 5 sources).[34, 45, 63, 66, 71]

In total, 19 studies reported across 24 references were included, and 7 study protocols were also included as "ongoing studies". Two studies[31, 34, 66] contributed data to two categories of studies (yield studies in the correct population and patient preference), and in one case the data were reported in two separate reports.[31, 66] One study (the NHSE CCE Pilot Study) was reported across a number of documents,[32, 40, 68, 78] some of which were obtained by personal communication.[40, 68, 78] One further patient preference study[45] was based on patients who had participated in one of the diagnostic test accuracy studies,[57] but the patient preference study has been counted as a separate study. Another patient preference study was reported across a conference abstract[63] and a full journal article,[71] and comprised two stages to the study. This study has been counted as one study.

Figure 4: PRISMA flow diagram of the study selection process



3.3.2 Studies of diagnostic test accuracy

3.3.2.1 Diagnostic test accuracy studies in scope-defined populations

Only one study[57] met the inclusion criteria for the review in terms of having recruited only symptomatic or surveillance populations. However, diagnostic test accuracy was only reported/calculable for "clinically significant disease", "any positive finding" and "significant polyps", all of which had somewhat uncertain definitions, as noted below.

The study is summarised in Table 4. It was a small (n=66) prospective single-centre study which recruited patients in Ireland who had been referred for the investigation of symptoms from primary care, and then vetted by a consultant gastroenterologist using NICE criteria at the time (prior to 2023). The authors state that these patients were an intermediate-to-low risk group. It is unclear what criteria were used to refer the patients to secondary care. The sample comprised some patients who had a FIT of >10µg/g (n=31/66) and some who did not have a FIT result (n=10/66), but results were not subgrouped by FIT results.

Risk of bias and applicability assessment using QUADAS-2:[43] Risk of bias assessment using the QUADAS-2[43] tool is presented in Table 3, and reasons for scores are presented in Appendix 4, Table 57.

The study was at high risk of bias because the reader of the reference standard was not blind to the index test result. It was at unclear risk of bias with respect to patient selection, as it was unclear if consecutive patients were enrolled, and at unclear risk of bias with respect to flow and timing, since it was not clear if COL was performed within 6 months for all patients. It was at low risk of bias with respect to the index test and there were no concerns about applicability of the index test or reference standard. The population may not represent the full spectrum of symptomatic patients (as it only included intermediate- to low-risk symptomatic patients) and so applicability of the patient selection was scored as high risk.

Table 3: Summary risk of bias and applicability as assessed by the EAG using the QUADAS-2 tool

Domain	Section	Signalling question	Ismail 2021[57]
Domain 1 **Patient selection**	Risk of bias summary scores	Could the selection of patients have introduced bias?	Unclear
Domain 2 **Index tests**		Could the conduct or interpretation of the index test have introduced bias?	Low
Domain 3 **Reference standard**		Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Domain 4 **Flow and timing**		Could flow and timing have introduced bias?	Unclear
Domain 1 **Patient selection**	Applicability scores	Is there concern that the included patients and settings do not match the review question?	**Symptomatic population:** High risk, may not be full spectrum of symptomatic patients **Surveillance population:** N/A
Domain 2 **Index tests**		Is there concern that the index test, its conduct, or interpretation differ from the review question?	Low
Domain 3 **Reference standard**		Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

NA - not applicable

Adequate or better bowel cleansing was achieved in 92% of patients, and the CCE completion rate was 76%. Sensitivity for clinically significant disease (definition unclear, see footnote to Table 4) was reported as 81% (95% CI not reported [NR], calculated by EAG:[81] 0.57-0.93) and specificity as 98% (95% CI NR, calculated by EAG:[81] 0.90-1.00), and for any positive finding (definition unclear, see footnote to Table 4) these values were 79% and 71%, respectively. The EAG calculated sensitivity and specificity for "significant polyps" which were defined in the paper as >3 polyps or one or more polyps >6mm. However, the paper referenced the ESGE guidelines, where these categories are defined as ≥3 polyps or one or more polyps ≥6mm. Based on data in Table 1 of the study publication, and a sentence in the discussion section of the paper noting that all significant polyps were identified by CCE, sensitivity and specificity for detecting significant polyps were calculated by the EAG as 100% (95% CI calculated by EAG:[81] 0.65-1.00) and 98% (95% CI calculated by EAG:[81] 0.91-1.00), respectively.

Table 4: Study characteristics and outcomes for the one study that met the population inclusion criteria

Author year Country Funding/CoI	Study design	Inclusion criteria % in-scope	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	Diagnostic test accuracy data Prevalence n/N (%) Sensitivity (95% CI) Specificity (95% CI)	Other outcomes
Ismail 2021[57] Ireland Authors had no CoI to declare	Prospective, single-centre	Patients aged from 18 to 80 years, referred from primary care for investigation of lower GI symptoms, who required a non-urgent COL based on vetting by a consultant gastroenterologist applying NICE criteria, were included. These patients are considered intermediate or low risk. 100%	77 66	45.8 (NR) 39 (58%) NR	**Significant polyps:*** Prev: 7/66 (11) Sens: 1 (0.65-1.00) Spec: 0.98 (0.91-1.00) **Clinically significant disease:**† Prev: 16/66 (24) Sens: 0.81 (0.57-0.93) Spec: 0.98 (0.90-1.00) **Any positive finding:**‡ Prev: 42/66 (68) Sens: 0.79 (0.65-0.89) Spec: 0.71 (0.51-0.85) **Colitis:** Prev: 7/66 (11) Sens: 43% Spec: NR	CCE completion: 76% Bowel cleansing (≥ adequate): 92%

COL - colonoscopy; Sens - sensitivity; spec - specificity; prev - prevalence; SD - standard deviation; GI - gastrointestinal; CoI - conflict of interest; NICE - National Institute for Health and Care Excellence

**Calculated based on the number of significant polyps on CCE (n=8), the number on COL (n=7) and the statement in the discussion section that CCE identified all significant polyps. Significant polyps were defined in the paper as "as per ESGE guidelines…> 3 lesions or a polyp greater than > 6mm based on polyp size estimation". However, ESGE guidelines define significant polyps as ≥3 polyps or one or more polyps ≥6mm. It is unclear if the text in the paper is a typo and in fact the correct definition was used.*

† The EAG was unable to locate a precise definition in the paper for "clinically significant disease",[57] but "clinically significant colonic findings" were defined as CRC, high-risk adenoma as defined by ESGE[27] and IBD, whilst "clinically significant small bowel disease" was defined as significant ulceration consistent with CD or NSAID enteritis, suspicious submucosal masses and P1 vascular lesions in subjects with a suspicion of bleeding. It is unclear if clinically significant disease relates to both these categories

‡The EAG was unable to locate a precise definition in the paper, but assumes that "any positive finding" may relate to any disease identified including polyps of any size, IBD, diverticulitis, haemorrhoids and potentially small bowel disease.

3.3.2.2 Diagnostic test accuracy studies in mixed populations

In this section, the review inclusion criteria were widened to include studies that report diagnostic test accuracy but recruited a mixed population of patients, at least some of whom are patients defined in the final NICE scope,[35] i.e., patients with lower GI signs or symptoms suggestive of CRC referred to secondary care, or patients undergoing post-polypectomy surveillance because of high-risk findings at their baseline COL (Widened 1, see Table 2). These studies are included in this assessment because there were no studies in the correct population that reported diagnostic test accuracy for polyps in the different size categories, and Ismail *et al*.[57] was a small single-centre study reporting limited data for some symptomatic patients only. Estimates of diagnostic accuracy are required for the EAG's economic model, and by restricting to studies that include at least some of the correct population (rather than including studies in screening populations, as done by other systematic reviews on CCE), estimates can be expected to have greater generalisability than studies with none of the protocol-defined patients. However, the generalisability of these studies may be low, especially where the proportion of relevant patients is low, and the similarity to patients reaching secondary care in the UK is uncertain.

Five studies[42, 46, 60, 75, 77] were included that reported on diagnostic test accuracy in a mixed population at least some of whom are patients defined in the final NICE scope.[35] All were published in peer-reviewed journal articles. Four studies[42, 57, 60, 75, 77] compared an index test of CCE to a reference standard of COL, whilst one study[46] compared CCE using white light to CCE using flexible spectral imaging colour enhancement, and compared both to COL. Only data for the test using white light have been extracted as the EAG's clinical experts confirmed that this is how the test is currently used in the NHS, and the NICE scope did not list the flexible spectral imaging colour enhancement variation as being relevant to current NHS practice.

Study and patient characteristics: The characteristics of the studies and patients are reported in Table 5. Three were prospective multicentre studies,[42, 57, 75, 77] and two were prospective single-centre studies.[46, 60] Studies were conducted in Israel,[75] Europe,[77] Germany,[60] the USA[42] and Japan.[46] Four of the studies[42, 60, 75, 77] were funded by the company (Given Imaging Ltd.) which manufactured the device at the time, whilst in one study[46] the authors declared that they had no conflicts of interest. The studies were all small, with the number of patients analysed being between 23[60] and 117.[77] Mean age was between 50[75] and 60 years[77] or not reported.[46] The proportion of patients who were female ranged from 27%[77] to 55%.[42] Data on ethnicity were not reported in four studies,[42, 60, 75, 77] though the study from Japan[46] noted that their sample was ethnically homogeneous, and the EAG suggests it is therefore likely to be comprised entirely of Japanese patients.

All five studies recruited a mixed population indicated for COL, but criteria differed between studies regarding some details (see Table 5). Across all the studies, the reasons for referral included personal

or family history of polyps, CRC screening, polyp surveillance, suspected IBD, and symptoms such as change in bowel habit, abdominal pain, rectal bleeding, or a positive FIT. One study[46] also included FIT-positive patients requiring colorectal tumour screening after upper GI tumour detection and patients with suspected colonic lesions based on other investigations, and may therefore have recruited a somewhat different population than the other studies. The percentage of patients likely to be within the scope of the assessment varied from 64%[77] to potentially as little as 11%.[46]

Bowel preparation and medications to encourage transit of the CCE through the gut were reported in four studies,[42, 60, 75, 77] all of which used a polyethylene glycol (PEG) laxative with a later bisacodyl suppository. A sodium phosphate booster was used in three studies,[60, 75, 77] and magnesium was used in one study.[42] Senna, a stimulant laxative, was used prior to PEG in two studies.[60, 77]

The criteria used to judge whether the polyps seen on CCE matched those on COL were also variable. All studies used polyp size to judge whether polyps matched, but some studies also mentioned location and morphology; it was not clear to the EAG if these criteria were applied to the analyses by size. In one study,[75] the polyp size on COL had to be in the same size category (≥6mm or ≥10mm) as the size on CCE, but the CCE measure provided by the RAPID software was uplifted by 50%. In two others,[60, 77] the CCE polyp size was estimated to be +/-50% of that measured by the software. In the fourth study,[42] the polyp size was estimated to be +/-50% of that measured by the software, whilst the COL measurement could also be +/-50%, and polyps were matched if the ranges overlapped. In the final study,[46] the size on CCE had to be 50-200% of that on COL.

Table 5: Study and patient characteristics of studies reporting diagnostic test accuracy in a mixed population at least some of whom are patients defined in the final NICE scope[35]

Author year Country Funding/CoI	Study design	Inclusion criteria	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	% in scope Indications for referral %	Bowel preparation methodology	Polyp matching criteria
Eliakim 2009[75] Israel Given Imaging	Prospective, multicentre	Patients (18–57 years of age) scheduled to undergo COL for either known or suspected colonic disease.	104 98	50 (NR) 34 NR	In-scope: 41% • Personal/family history: 34 • CRC screening: 32 • Hematochezia or FOBT+: 21 • Symptoms (diarrhoea, constipation, abdominal pain): 17 • IDA: 3	PEG + NaP + bisacodyl	Polyp in same size category (categories were ≥6mm and ≥10mm), on COL and CCE, with 50% increase in size for CCE reading.
Spada 2011[77] Europe Given Imaging	Prospective, multicentre	Patients (18-80 years of age) scheduled to undergo COL for either known or suspected colonic disease.	117 109	60 (9) 38 NR	In-scope: 64% • Personal history of polyps/positive findings: 44 • Recent change in bowel habits: 23 • CRC screening: 21 • Rectal bleeding/ haematochezia: 20 • Abdominal pain: 15 • Positive FIT: 6	Senna + PEG + NaP + Bisacodyl	Polyp on COL in same size category (categories were ≥6mm and ≥10mm), as polyp on CCE+/- 50%.

Author year **Country** **Funding/CoI**	**Study design**	**Inclusion criteria**	**N recruited** **N patients analysed**	**Mean age (SD)** **N Female (% female)** **Ethnicity**	**% in scope** **Indications for referral %**	**Bowel preparation methodology**	**Polyp matching criteria**

Hagel 2014[60]
Germany
Given Imaging
	Prospective, single centre	Patients scheduled to undergo COL for either known or suspected colonic disease.	24
			23
				51 (NR)
				42
				NR
					In-scope: 29% (polyp surveillance)
					• CRC screening
					  ○ Positive family history: 22
					  ○ No increased risk: 33
					• Polyp surveillance: 29
					• Suspected inflammatory bowel disease: 8
					• Surveillance COL in UC: 8
						Senna + PEG + NaP + bisacodyl	Size, location and morphology considered. Polyp on COL same size as CCE +/-50%.

Morgan 2016[42] USA Given Imaging	Prospective, multicentre	Participants (18-70 years of age) with indications for conventional COL, including clinical symptoms (e.g., rectal bleeding, haematochezia, melena, positive FOBT), recent change in bowel habits patients ≥50 years, a polyp ≥10 mm on a prior radiographic test or sigmoidoscopy, a personal history of polyp(s) ≥6 mm in size that was removed at least 3 years ago, or CRC screening if age was ≥60 years.	51 50	60 (NR) 55 NR	In-scope: unclear since some patients had more than one indication, possibly 44% (i.e., those not undergoing average-risk screening) • Average-risk screening (n=28) • Polyp surveillance (n=11) • Change in bowel habits (n=16) • Rectal bleeding (n=7) • Abdominal pain (n=6) • Positive FIT (n=1)	PEG + Magnesium + bisacodyl	Size range overlapped based on COL+/-50% and CCE+/-50%; location same or adjacent colonic segment

Author year Country Funding/CoI	Study design	Inclusion criteria	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	% in scope Indications for referral %	Bowel preparation methodology	Polyp matching criteria
Omori 2024[46] Japan Authors had no CoI to declare	Prospective, single centre	FIT+ patients requiring colorectal tumour screening after upper GI tumour detection, suspected colonic lesions based on other investigations, and symptoms such as haematochezia, long-term diarrhoea, or constipation in whom the need for colonic investigation was determined by a physician.	91 89	Mean age NR, Median 66 (range 32-79) 27 100% Japanese (states "ethnically homogenous Japanese sample)	In scope: unclear as category definitions lack detail, potentially as few as 11% or as many as 72% • Positive FIT: 39 • Screening of oesophageal and gastric tumours: 25 • Follow-up of colorectal polyps: 22 • Haematochezia: 7 • Abdominal pain: 3 • Elevated tumour marker level: 2 • diarrhoea: 1	NR	Macroscopic type consistent; location same or adjacent colonic segment; and size on CCE 50-200% that of COL.

CCE - colon capsule endoscopy; CoI - conflict of interest; COL - colonoscopy; CRC - colorectal cancer; UC - ulcerative colitis; F - female; FIT - faecal immunochemical test; FOBT+ - faecal occult blood test positive; GI - gastrointestinal; M, male; NaP - sodium phosphate; PEG - polyethylene glycol; SD - standard deviation; N - number; NR - not reported.

Risk of bias and applicability assessment using QUADAS-2:[43] Risk of bias assessment using the QUADAS-2[43] tool is presented in Table 6, and a table including the scores for each signalling question with reasons for scores is presented in Appendix 4, Table 57.

No single study scored low risk on all items across risk of bias and applicability domains. Three studies[42, 46, 60] were unclear with respect to patient selection due to a lack of clarity about whether a consecutive or random sample of patients was recruited. Two scored high risk, one due to the exclusion of patients over 57 years of age,[75] and another due to not recruiting a consecutive sample.[77] The conduct of the index test was at low risk of bias in all studies as the index test was conducted in secondary care and interpreted by clinicians using proprietary software and without knowledge of the reference standard result. The reference standard was at low risk of bias in all studies as clinicians were blinded to the index test results and all patients received the same reference standard. Flow and timing were at low risk of bias in four studies[42, 60, 75, 77] because although some patients were excluded, the reasons were provided and were unlikely to be associated with test accuracy, e.g., the recorder failed or the patient could not swallow the device. In one study,[46] two patients with ≥30 polyps were excluded from the analysis, and this was scored as high risk as the exclusion reason was likely to be associated with test accuracy. Applicability of the index test and reference standard were scored at low risk of bias; however, there was concern for all studies that the patients did not match the review question due to the inclusion of patients outside the scope of the assessment, and all scored high risk for this item.

Table 6: Summary risk of bias and applicability as assessed by the EAG using the QUADAS-2 tool

Domain	Section	Signalling question	Eliakim 2009[75]	Spada 2011[77]	Hagel 2014[60]	Morgan 2016[42]	Omori 2024[46]
Domain 1 **Patient selection**	Risk of bias summary scores	Could the selection of patients have introduced bias?	High	High	Unclear	Unclear	Unclear
Domain 2 **Index tests**		Could the conduct or interpretation of the index test have introduced bias?	Low	Low	Low	Low	Low
Domain 3 **Reference standard**		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low	Low	Low	Low	Low
Domain 4 **Flow and timing**		Could flow and timing have introduced bias?	Low	Low	Low	Low	High
Domain 1 **Patient selection**	Applicability scores	Is there concern that the included patients and settings do not match the review question?	High	High	High	High	High
Domain 2 **Index tests**		Is there concern that the index test, its conduct, or interpretation differ from the review question?	Low	Low	Low	Low	Low
Domain 3 **Reference standard**		Is there concern that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low

Note: Reasons for scores can be found in Appendix 4

Outcomes: Data relating to outcomes are reported in Table 7, Table 8 and Table 10. As can be seen from these tables, not all studies reported all outcomes.

Bowel preparation: All studies reported the proportion of patients with adequate bowel preparation, which ranged from 61%[42] to 91%.[46]

Completion rates and retentions: One study[60] reported the completion rate which was 74% (full colonic imaging) whilst another reported a value of 89%[46] (excretion within the battery life). Two reported the number of patients who excreted the capsule within 10 or 8 hours of ingestion (i.e., both of which are theoretically within the battery life), and these values were 64%[42] and 88%,[77] respectively. Capsule retentions were not reliably estimable in three studies because COL was performed on the same day[42] or within 8 or 12 hours,[75, 77] and was used to remove any CCE which had not been excreted by that point. One other study reported no retentions,[60] whilst the last study did not report retentions.[46]

There was some heterogeneity amongst studies regarding the inclusion of patients with incomplete CCEs in the analysis. In one study,[75] at least some incomplete CCEs were excluded from the analysis, in two[60, 77] some incomplete CCEs were included and some were excluded, and in two[42, 46] incomplete CCEs appeared to be included in the analysis (see Table 7, including the footnotes).

Other AEs and technical failures: Two studies reported that the capsule or reader encountered a technical failure in 1%[75] and 3%[77] of cases. Technical failures were not mentioned in the other three studies.[42, 46, 60] Three studies[60, 75, 77] reported on AEs of any seriousness related to bowel preparation; these occurred in ≤5% of patients, and included headaches, nausea, vomiting and abdominal pain. One study[42] reported only serious AEs and noted that none were thought to be related to CCE. One study[77] reported fatigue in 2% of patients.

Test uptake: It was not possible to measure test uptake in the context of an experimental study, since refusal to enrol may be related to the intervention and/or due to factors introduced by the study design, such as having to undergo two procedures (CCE and COL).

Diagnostic test accuracy for detecting polyps: Per-patient analyses

Across the included studies, data on the diagnostic test accuracy of CCE for detecting polyps were reported for size categories of "any size", <6mm, ≥6mm, 6-9mm, and ≥10mm.

Table 7: Completion rates, withdrawals, AEs including retentions and technical failures

Author year	Number recruited	Not analysed with reasons	N analysed	Adequate bowel cleansing (%)	Completion rates n/N (%)* Incomplete CCE included in analysis?	Retentions n/N (%)*	Technical failure of capsule or recorder n/N (%)*	AEs related to bowel preparation n/N (%)*	Other AEs n/N (%)*
Eliakim 2009[75]	104	N=6 Did not complete the bowel preparation instructions: 2 Withdrew from the study: 1 Could not ingest the capsule: 1 Ran out of battery before reaching colon: 1 Technical failure: 1	98	78	NR At least some incomplete excluded§	Not estimable†	1/103 (1)	Mild-moderate headaches/nausea: 5 (5) mild vomiting: 2 (2)	None reported
Spada 2011[77]	117	N=8 Inability to swallow the capsule: 1 Technical failure of the data recorder: 2 Capsule technical failure: 2 Withdrew from the study: 1 Capsule remained in the cecum during the procedure: 2	109	81	NR Excretion within 10 hours: NR (88) Variable§	Not estimable†	4/116 (3)	Vomiting, nausea and/or abdominal pain: 5/116 (4)	Fatigue: 2/116 (2)
Hagel 2014[60]	24	N=1 Capsule did not reach the colon: 1	23	90	17/23 (74) Variable§	0/23 (0)	NR	Headache: 1/23 (4)	0 (0)
Morgan 2016[42]	51	N=1 1 withdrew from the study before capsule ingestion.	50	61	Within 8 hours of ingestion: 32/50 (64) Included§	Not estimable†	NR	Serious AEs: 0 (0)‡	0 (0)
Omori 2024[46]	91	N=2 Excluded 2 patients with 30 or more lesions as impossible to match	89	91	Within battery life: 89% Included§	NR	NR	NR	NR

CCE - colon capsule endoscopy; N - number; AE - adverse event; NR - not reported
** As a proportion of those who did not withdraw from the study*
*†True retention rate compared to clinical practice, where more time may be allowed for capsule egestion, was not estimated due to timing of COL, which was: **Eliakim et al.,**[75] COL performed within 8 hours of capsule ingestion; **Spada et al.,**[77] COL performed 10-12 hours after CCE ingestion; **Morgan et al.,**[42] COL performed on same day.*
‡Also reported mild abdominal bruising (n=1), and moderate abdominal pain (n=1), both considered unlikely to be related to the study by the investigators.
*§ **Eliakim et al.,**[75] 1 patient excluded because capsule remained in the caecum, does not report if any other "incomplete but diagnostic" CCEs included in the efficacy analysis; **Spada et al.,**[77] 2 patients excluded because capsule remained in caecum, but in three cases the CCE impacted a tumour meaning the CCE was incomplete but diagnostic, and these patients appear to have remained in the analysis; **Hagel et al.,**[60] 1 patient excluded because the capsule did not leave the stomach for 4 hours and did not reach the colon within battery life, six other patients with incomplete CCE were included in the analysis; **Morgan et al.,**[42] incomplete CCEs appear to have been included since the one FN was due to an incomplete CCE, where the capsule was removed after 9 hours, prior to entering the rectum; **Omori et al.,**[46] all patients included in the analysis, despite completion rate of 89%.*

Table 8: Per patient sensitivity and specificity for polyps

Author year	Inclusion criteria (% in scope)	n/N with target condition (%)	Reference standard	Polyp matching criteria	Sensitivity % (95% CI)	Specificity % (95% CI)
Target condition: polyps of any size, per patient						
Hagel 2014[60]	Scheduled to undergo COL for known or suspected colonic disease, age not specified	16/23 (70)	COL	Same size as CCE +/-50%. Size, location and morphology considered.	82 (62-100)	86 (60-100)
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	75/89 (84)	COL	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	79 (75-83)	43 (23-65)
Target condition: Polyps <6mm, per patient						
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	58/89 (65)	COL	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	55 (48-62)	65 (50-77)
Target condition: Polyps ≥6mm, per patient						
Eliakim 2009[75]	Scheduled to undergo COL for known or suspected colonic disease: age 18-57 years	18/98 (19)	COL	Same size category, 50% increase in size for CCE reading.	89 (70-97)*	76 (72-78)*
Spada 2011[77]	Scheduled to undergo COL for known or suspected colonic disease: age 18-80 years	45/109 (41)	COL	Same size category, polyp on CCE+/-50%.	84 (74-95)	64 (52-76)
Morgan 2016[42]	Symptomatic, screening or surveillance patient, with indication for COL	14/50 (30)	COL	Size range overlapped, COL+/-50%, CCE+/-50%. Location same or adjacent colonic segment	93 (69-99)†	78 (62-88)†
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	58/89 (65)	COL	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	78 (70-84)	55 (41-67)

Author year	Inclusion criteria (% in scope)	n/N with target condition (%)	Reference standard	Polyp matching criteria	Sensitivity % (95% CI)	Specificity % (95% CI)
Target condition: Polyps 6-9mm, per patient						
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	35/89 (39)	COL	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	63 (50-74)	76 (68-83)
Target condition: Polyps ≥10mm, per patient						
Eliakim 2009[75]	Scheduled to undergo COL for known or suspected colonic disease: age 18-57 years	8/98 (8)	COL	Same size category, 50% increase in size for CCE reading.	88 (56-98)	89 (86-90)
Spada 2011[77]	Scheduled to undergo COL for known or suspected colonic disease: age 18-80 years	32/109 (29)	COL	Same size category, polyp on CCE+/-50%.	88 (76-99)	95 (90-100)
Morgan 2016[42]	Symptomatic, screening or surveillance patient, with indication for COL	6/50 (12)	COL	Size range overlapped, COL+/-50%, CCE+/-50%. Location same or adjacent colonic segment	100 (61-100)†	91 (79-96)†
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	34/89 (38)	COL	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	79 (68-85)	87 (80-92)

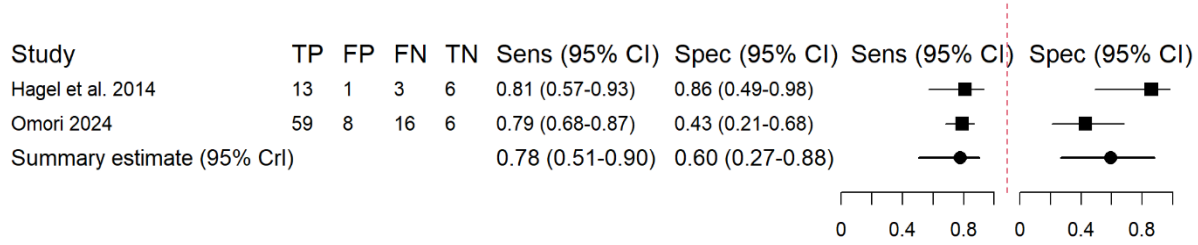
CCE - colon capsule endoscopy; CI - confidence interval; COL - colonoscopy; CRC - colorectal cancer; FIT - faecal immunochemical test; GI - gastrointestinal; n or N - number
**A small number (n=2) patients underwent a second COL. The results reported in this table relate to the results of the first COL. The paper reported that two patients underwent a second COL; in one case the capsule finding (and COL miss) was confirmed, and in the second case the capsule finding (and COL miss) was confirmed although second COL indicated a polyp size of 8 mm.*
† The EAG calculated these values based on the results of the first COL. The sensitivity and specificity reported in the paper were based on an optional repeat COL for those with a CCE-detected false-positive. One patient had a second COL which confirmed CCE findings had been missed by the first COL. Taking this into account, sensitivity and specificity reported in the paper were 93.3% (95% CI, 66.0-99.7) and 80% (95% CI, 62.5-90.9), respectively, for polyps ≥6mm, and 100% (95% CI, 56.1-100.00) and 93.0% (95% CI, 79.9-98.2) respectively for polyps ≥10mm.

Prevalence, sensitivity and specificity of CCE for identifying polyps of any size:

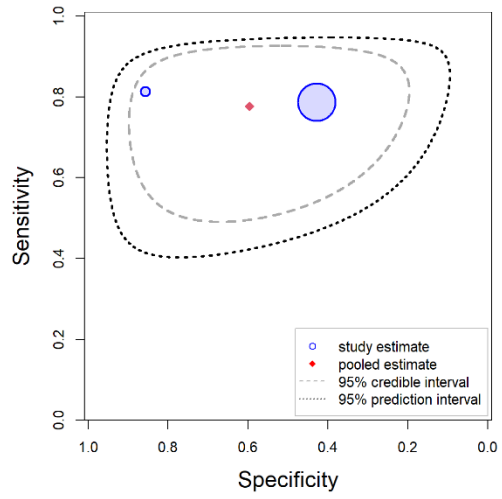
Table 8 presents the characteristics and results of the two studies[46, 60] that reported test accuracy for identification of polyps of any size. Prevalence was 70%[60] and 84%.[46] Sensitivity was 79%[46] and 82%,[60] whilst specificity was 43%[46] and 86%,[60] respectively. A meta-analysis of these data is presented in Figure 5. The pooled estimates of sensitivity and specificity were 0.78 (95% CrI: 0.51, 0.90) and 0.60 (95% CrI: 0.27, 0.88), respectively. The between-study SD (see Table 9) was estimated to be 0.42 (95% CrI: 0.02, 1.77) for logit sensitivity and 0.79 (95% CrI: 0.04, 2.19) for logit specificity. The between-study correlation between logit sensitivity and specificity was estimated to be -0.48 (95% CrI: -0.97, -0.02). Figure 5b presents the SROC plot. The blue circles represent the observed sensitivity and specificity in each study, with larger circles indicating larger sample sizes. The red diamond shows the estimated average sensitivity and specificity. The grey dashed line indicates a 95% credible region. The black dashed line represents a 95% prediction region, providing a visual illustration of the between-study heterogeneity. The 95% PrI was estimated to be 0.3-0.95 for sensitivity and 0.1-0.96 for specificity. The results suggest large between-study variation.

Figure 5: a) Forest plot and b) SROC plot of CCE for polyps of any size

a)



b)



CI - confidence interval; CrI - credible interval

Prevalence, sensitivity and specificity of CCE for identifying polyps <6mm in size:

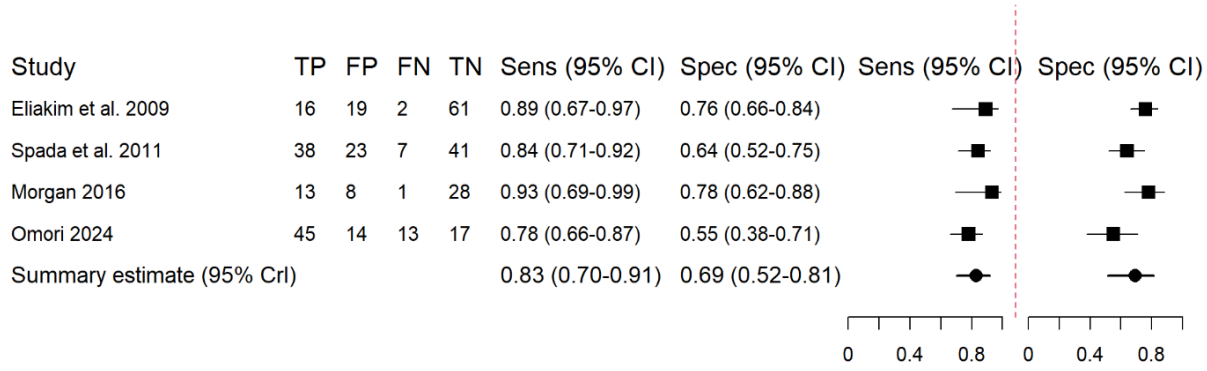
Table 8 presents the characteristics and results of the one study[46] which reported test accuracy for the identification of polyps <6mm in size. Prevalence was 65%, sensitivity was 55% (95% CI 48-62%) and specificity was 65% (95% CI 50-77%). No synthesis was possible because only one study reported the outcome.

Prevalence, sensitivity and specificity of CCE for identifying polyps ≥6mm in size:

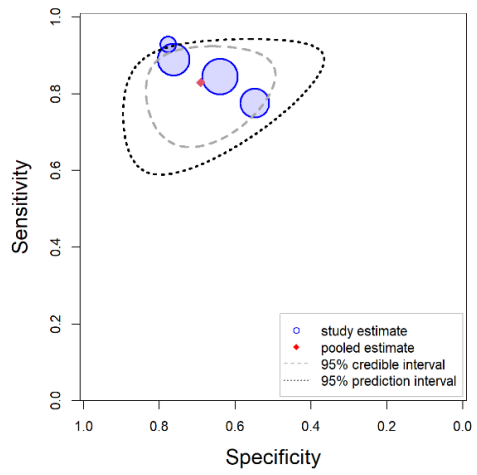
Table 8 presents the characteristics and results of the four studies[42, 46, 75, 77] that reported test accuracy for the identification of polyps ≥6mm in size. Prevalence ranged from 19%[75] to 65%,[46] indicating that populations are likely heterogeneous in clinical composition and reflecting the differing recruitment criteria. Sensitivity ranged from 78%[46] to 93%[42] and specificity from 55%[46] to 78%.[42] A meta-analysis of these data is presented in Figure 6. The pooled estimates of sensitivity and specificity were 0.83 (95% CrI: 0.70, 0.91) and 0.69 (95% CrI: 0.52, 0.81). The between-study SD (see Table 9) was estimated to be 0.33 (95% CrI: 0.01, 1.45) for logit sensitivity and 0.41 (95% CrI: 0.02, 1.67) for logit specificity. The between-study correlation between logit sensitivity and specificity was estimated to be -0.42 (95% CrI: -0.96, -0.02). Figure 6b presents the SROC plot. The blue circles represent the observed sensitivity and specificity in each study, with larger circles indicating larger sample sizes. The red diamond shows the estimated average sensitivity and specificity. The grey dashed line indicates a 95% credible region. The black dashed line represents a 95% prediction region, providing a visual illustration of the between-study heterogeneity. The 95% PrI was estimated to be 0.53-0.96 for sensitivity and 0.32-0.91 for specificity. The results suggest moderate between-study variation.

Figure 6: a) Forest plot and b) SROC plot of CCE for polyps ≥6mm in size

a)



b)



CI - confidence interval; CrI - credible interval

Prevalence, sensitivity and specificity of CCE for identifying polyps 6-9mm in size:

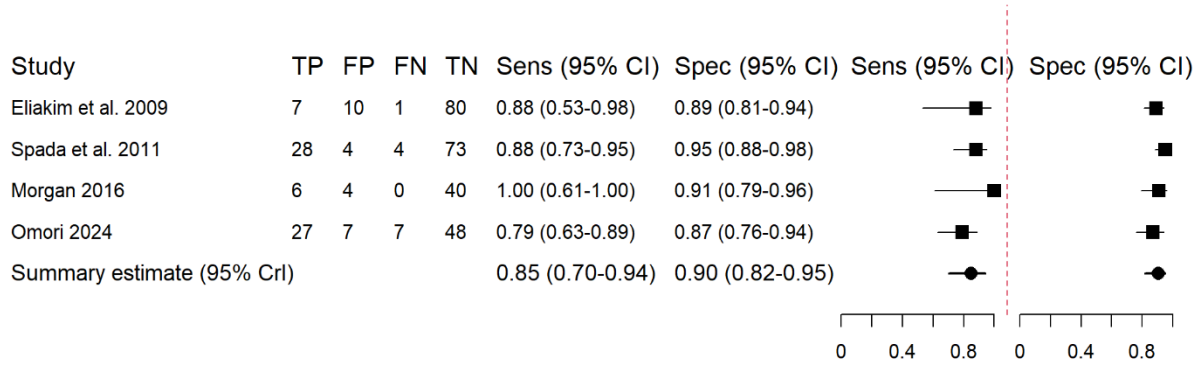
Table 8 presents the characteristics and results of the one study[46] that reported test accuracy for the identification of polyps 6-9mm in size. Prevalence was 39%, sensitivity was 63% (95% CI 50-74%) and specificity was 76% (95% CI 68-83%). No synthesis was possible because only one study reported the outcome.

Prevalence, sensitivity and specificity of CCE for identifying polyps ≥10mm in size:

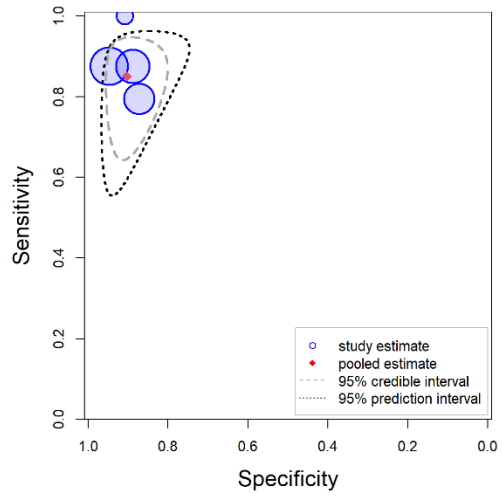
Table 8 presents the characteristics and results of the four studies[42, 46, 75, 77] that reported test accuracy for the identification of polyps ≥10mm in size. Prevalence ranged from 8%[75] to 38%,[46] indicating that populations are likely heterogeneous in clinical composition and reflecting the differing recruitment criteria. Sensitivity ranged from 79%[46] to 100%[42] and specificity ranged from 87%[46] to 95%.[77] A meta-analysis of these data is presented in Figure 7. The pooled estimates of sensitivity and specificity were 0.85 (95% CrI: 0.70, 0.94) and 0.90 (95% CrI: 0.82, 0.95), respectively. The between-study SD (see Table 9) was estimated to be 0.41 (95% CrI: 0.02, 1.67) for logit sensitivity and 0.32 (95% CrI: 0.02, 1.35) for logit specificity. The between-study correlation between logit sensitivity and specificity was estimated to be -0.47 (95% CrI: -0.97, -0.02). Figure 7b presents the SROC plot. The blue circles represent the observed sensitivity and specificity in each study, with larger circles indicating larger sample sizes. The red diamond shows the estimated average sensitivity and specificity. The grey dashed line indicates a 95% credible region. The black dashed line represents a 95% prediction region, providing a visual illustration of the between-study heterogeneity. The 95% PrI was estimated to be 0.51-0.97 for sensitivity and 0.69-0.97 for specificity. The results suggest moderate between-study variation.

Figure 7: a) Forest plot and b) SROC plot of CCE for polyps ≥10mm in size

a)



b)



CI - confidence interval; CrI - credible interval

Sensitivity analyses for DTA syntheses

Sensitivity analyses were conducted; results are presented in Table 9. Sensitivity analysis 1 was conducted to exclude Omori *et al.* because it had different inclusion criteria than the other studies, including patients with known upper GI tumours and suspected lesions based on other investigations; these patients are outside of the scope of this assessment, and none of the other studies included them. After removing Omori *et al.* from the analysis (sensitivity analysis 1), the point estimate of pooled sensitivity and specificity increased for both polyps of ≥6mm and ≥10mm. When the non-informative prior distribution is used for the same studies (sensitivity analysis 2), the CrIs are wide.

Table 9: Sensitivity analyses: summary of pooled sensitivities and specificities

Analysis	Pooled sensitivity (95% CrI) [95% PrI]			Pooled specificity (95% CrI) [95% PrI]		
	Any size	**≥6mm**	**≥10mm**	**Any size**	**≥6mm**	**≥10mm**
Base case (informative prior)	0.78 (0.51,0.90) [0.3,0.95]	0.83 (0.70, 0.91) [0.53, 0.96]	0.85 (0.70, 0.94) [0.51, 0.97]	0.60 (0.27, 0.88) [0.1 ,0.96]	0.69 (0.52, 0.81) [0.32, 0.91]	0.90 (0.82, 0.95) [0.69, 0.97]
Sensitivity analysis 1 (informative prior)	N/A	0.86 (0.68, 0.94) [0.49, 0.97]	0.88 (0.68, 0.97) [0.47,0.98]	N/A	0.72 (0.53, 0.85) [0.35, 0.92]	0.91 (0.78, 0.96) [0.62, 0.98]
Sensitivity analysis 2 (vague prior)	0.76 (0.26, 0.93) [0.02, 0.99]	0.83 (0.57, 0.93) [0.22, 0.98]	0.85 (0.52, 0.96) [0.1, 0.99]	0.60 (0.14, 0.94) [0.00, 1.00]	0.69 (0.43, 0.84) [0.15, 0.96]	0.90 (0.72, 0.95) [0.43, 0.99]
	Standard deviation of logit sensitivity (95% CrI)			**Standard deviation of logit specificity (95% CrI)**		
	Any size	**≥6mm**	**≥10mm**	**Any size**	**≥6mm**	**≥10mm**
Base case (informative prior)	0.42 (0.02, 1.77)	0.33 (0.01, 1.45)	0.41 (0.02, 1.67)	0.79 (0.04, 2.19)	0.44 (0.03, 1.44)	0.32 (0.02, 1.35)
Sensitivity analysis 1 (informative prior)	N/A	0.40 (0.02, 1.70)	0.50 (0.02, 1.89)	N/A	0.39 (0.02, 1.52)	0.41 (0.02, 1.63)
Sensitivity analysis 2 (vague prior)	0.94 (0.03, 4.49)	0.49 (0.02, 3.30)	0.70 (0.02, 4.1)	1.97 (0.15, 4.75)	0.57 (0.03, 2.90)	0.43 (0.02, 2.85)
	Correlation between logit sensitivity and specificity (95% CrI)					
	Any size	**≥6mm**	**≥10mm**			
Base case (informative prior)	-0.48 (-0.97, -0.02)	-0.42 (-0.96, -0.02)	-0.47 (-0.97, -0.02)			
Sensitivity analysis 1 (informative prior)	N/A	-0.47 (-0.97, -0.02)	-0.5 (-0.98, -0.02)			
Sensitivity analysis 2 (vague prior)	-0.49(-0.97,-0.02)	-0.43 (-0.96, -0.02)	-0.48 (-0.97, -0.02)			

CrI - credible interval; PrI - prediction interval; N/A - not applicable

Diagnostic test accuracy for detecting polyps: Per-polyp analyses

Only two studies[46, 60] reported per-polyp analyses (see Table 10). Data were reported for size categories of "any size", <6mm, ≥6mm, 6-9mm, and ≥10mm. Hagel *et al*.[60] reported both sensitivity and specificity, but because the number of FP *polyp*s and the number of TN *people* were reported, the EAG believes that true specificity cannot be calculated. Sensitivity in this study ranged from 100% for polyps <6mm to 72% for polyps 6-9mm. Notably, there was no clear trend towards better or worse sensitivity based on size of the polyp. Two different values were reported for sensitivity for any polyp, which was reported as 80% in a table, but 91% in the text of the article; the EAG is uncertain which value is correct. In Omori *et al*.,[46] the sensitivity ranged from 53% for polyps <6mm to 81% for polyps ≥10mm. In this study, sensitivity increased as the size of the polyps increased.

Table 10: Per-polyp sensitivity and specificity for polyps

Author year	Inclusion criteria (% in scope)	Polyp size	N people in analysis	Number polyps detected on COL	Polyp matching criteria	Sensitivity % (95% CI)	Specificity % (95% CI)
Hagel 2014[60]	Scheduled to undergo COL for known or suspected colonic disease, age not specified	<6mm	23	16	Same size as CCE +/-50%. Size, location and morphology considered.	100	83*
		6-9mm	23	17		72	91*
		≥10mm	23	11		75	100*
		any size	23	44		80 Also reported as 91 (85-100)	94 Also reported as 68 (36-98)
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	<6mm	89	156	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	53	NR
		6-9mm	89	54		65	NR
		≥10mm	89	47		81	NR

CCE - colon capsule endoscopy; CI - confidence interval; COL - colonoscopy; FIT - faecal immunochemical test; GI - gastrointestinal; n or N - number

** To calculate specificity, the authors of Hagel et al.[60] counted patients who had no disease on both tests as TNs, whilst the number of polyps identified by CCE but not by COL were counted as FPs. The EAG does not believe this is true specificity.*

Diagnostic test accuracy and detection rates for detecting adenomas, CRC and IBD: Per-patient analyses

Data on adenomas were limited, with only one study reporting sensitivity and specificity for adenomas (see Table 11), and two studies[75, 77] reporting only detection rate (calculated in the same way as sensitivity, i.e., TP/[TP+FN], see Table 12). Matching specificity data were not provided and it was unclear what was counted as a positive CCE test across the studies (e.g., polyp of that size category, polyp of any size, was clinical judgement used?) meaning that specificity could not be calculated by the EAG.

Across the three studies, sensitivity for adenomas was quite variable, with values for polyps ≥6mm ranging from 79%[46] to 100%,[75] and for adenomas ≥10mm ranging from 81%[46] to 100%.[75] Sensitivity for adenomas <6mm was relatively low, at 59% (95% CI 49-67%).[46]

Specificity (n=1 study)[46] ranged from 65% (95% CI 50-78%) for adenomas any size, to 91% (95% CI 86-84%) for adenomas ≥10mm.

Table 11: Per patient sensitivity and specificity for adenomas

Author year	Inclusion criteria (% in scope)	Polyp size	n/N with polyp (%)	Reference standard	Polyp matching criteria	Sensitivity % (95% CI)	Specificity % (95% CI)
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	Adenoma any size	63/89 (71)	COL + biopsy	Size on CCE 50-200% that of COL. Macroscopic type consistent; location same or adjacent colonic segment.	76 (70-82)	65 (50-78)
		Adenoma <6mm	44/89 (49)			59 (49-67)	80 (70-88)
		adenoma 6-9mm	28/89 (31)			68 (53-80)	70 (64-76)
		adenomas ≥6mm	47/89 (53)			79 (69-86)	71 (61-80)
		adenomas ≥10mm	21/89 (24)			81 (65-91)	91 (86-94)

CCE - colon capsule endoscopy; CI - confidence interval; COL - colonoscopy; FIT - faecal immunochemical test; GI - gastrointestinal; n or N - number

Two studies reported detection rate (sensitivity) for CRC, but event rates were low (n=1 and n=3 CRCs).[75, 77] In Eliakim *et al.*,[77] the single CRC was detected by both CCE and COL, which can be calculated to be 100% sensitivity. In Spada *et al.*,[77] all three CRCs were detected by CCE. Two studies[75, 77] reported data on erythema/inflammation with sensitivity calculated by the EAG as 36% and 75%. One further study[60] noted that CCE detected one case of IBD which was confirmed by COL, but did not state how many cases were identified by COL.

Table 12: Adenomas, CRC and other bowel pathologies detected

Author year	Inclusion criteria (% in scope)	Adenomas n CCE / N COL (% (95% CI))		CRC n CCE / N COL (%)	IBD n CCE / N COL (%)
		≥6mm	≥10mm		
Eliakim 2009[75]	Scheduled to undergo COL for known or suspected colonic disease: age 18-57 years	11/11 (100)	5/5 (100)	1/1 (100)	3/4*(75)
Spada 2011[77]	Scheduled to undergo COL for known or suspected colonic disease: age 18-80 years	35/39 (90 (80-99)	28/30 (93 (84-100)	3/3 (100)	4/11 (36)* (CCE detected 7 cases not detected by COL)
Hagel 2014[60]	Scheduled to undergo COL for known or suspected colonic disease, age not specified	NR	NR	NR	UC inflammation: 1†
Morgan 2016[42]	Symptomatic, screening or surveillance patient, with indication for COL	NR	NR	No cancers detected by either method	NR (possibly no events)
Omori 2024[46]	Upper GI tumour with FIT+, or suspected colonic lesions based on other investigations, symptoms	NR	NR	NR	NR

CRC - colorectal cancer; CCE - colon capsule endoscopy; COL - colonoscopy; IBD - inflammatory bowel disease; GI - gastrointestinal; FIT - faecal immunochemical test; CI - confidence interval; N - number; NR - not reported
** Defined as erythema or inflammation*
†Confirmed by other test (COL, FSIG), but unclear if any cases were missed by CCE.

3.3.3 Studies reporting data on diagnostic yield

3.3.3.1 Studies in symptomatic and surveillance populations defined in the scope

In this section, the review inclusion criteria were widened to include studies that report yield but not diagnostic test accuracy (Widened 2, see Table 2). These studies had to recruit the populations listed in the final NICE scope.[35] Yield could be either the number of polyps and other pathologies detected by CCE (i.e., CCE TPs+FPs), or the number detected by CCE and confirmed by COL (TPs only). These studies are included in this assessment because they are likely to have high generalisability to the decision problem and they provide data on parameters of importance to the EAG's economic model apart from diagnostic test accuracy (see Section 4.3).

Four studies were included: the NHSE CCE Pilot Study,[32] ScotCap,[31] the Wales CCE Pilot Study[34] and a study from Barnsley (England) conducted during the COVID-19 pandemic (Mahdi *et al.* 2023).[33] The NHSE CCE Pilot Study had not fully reported at the time of writing, with only a conference abstract

available in the public domain.[32] Additional documentation (a protocol and a statistical analysis plan)[68, 78] and a bespoke analysis[40] of the dataset were provided to the EAG in confidence to inform the economic model, and data from this study are marked as academic-in-confidence (AIC). ScotCap has reported in full,[31] whilst only a conference abstract was identified for the Barnsley study.[33] No published report relating to the Wales CCE Pilot Study was identified; a poster presentation and slide set were accessed via a website about the project.[34]

Study and patient characteristics: The characteristics of the studies and patients are reported in Table 13. Two were prospective multicentre studies,[31, 32, 40, 68, 78] one was not reported,[34] and one was a retrospective single-centre study.[33] Two studies[32, 33, 40, 68, 78] were conducted in England, one in Wales[34] and one in Scotland.[31] The number of patients analysed was 76,[33] 509,[31] [redacted][32, 40, 68, 78] and not reported,[34] with two studies[31, 32, 40, 68, 78] recruiting both symptomatic and surveillance populations. Data on mean age and the percentage of patients who were female are reported in Table 13.

All four studies included symptomatic patients, but the recruitment criteria differed. The NHSE CCE Pilot Study recruited [redacted]. Even though the NG12 criteria changed in 2023, the selection of patients should be similar to current practice because all patients received a FIT, as is now recommended by NG12.[82] The NHSE CCE Pilot Study also included [redacted] As it is currently unclear how patients would be selected for CCE in clinical practice, this may or may not affect generalisability of the study results. Mahdi *et al.*[33] recruited symptomatic patients who met NG12 criteria with a FIT score of 10-100µg/g, who had been given a CCE; it is unclear whether the choice of CCE was based on clinical judgement [redacted] The Wales Pilot Study[34] appears to have recruited patients with symptoms and a FIT of <10µg/g, designated "low-risk", and it was likely, based on suggested criteria in the pilot study documentation,[83] they were recruited using NG12 criteria. ScotCap[31] recruited patients referred according to Scottish referral criteria, which differ somewhat to the NG12 criteria, and patients could have a FIT or no FIT. The data from this study are therefore likely to have lower generalisability to the decision problem but are provided for completeness.

Two studies[31, 32, 40, 68, 78] recruited surveillance patients, [redacted] MacLeod *et al.*[31] recruited patients who were due to undergo surveillance for personal or family history of CRC; history of colonic polyposis; or Lynch syndrome, which is wider than the NICE scope

(n=69/509 in total). Whilst this study does not strictly meet the inclusion criteria, it has been reported here for completeness as the study also reported a subgroup of symptomatic patients and it is included in the patient preference synthesis.

Table 13: Study and patient characteristics of studies reporting yield in populations listed in the NICE scope[35]

Author year **Country** **Funding/CoI**	**Study design**	**Inclusion criteria/ Indication**	**N patients analysed**	**Mean age (SD)** **N Female (% female)** **Ethnicity**	**Bowel preparation methodology**	**Polyp matching criteria**
MacLeod 2022[31] (ScotCap) Scotland Scottish Government	Prospective, multicentre clinical evaluation	Over 18 years of age; able to provide consent; and either 1 or 2: 1. Symptomatic: Referred from primary care with lower GI symptoms and assessed as requiring a COL by a secondary-care consultant. With or without FIT. 2. Surveillance: Due surveillance COL in the month before, during and month after recruitment period for: personal or family history of CRC; history of colonic polyposis; HNPCC†	Total: 509 1) 316 2) 193	Symptomatic: 58.9 (11.9) 56.6% NR Surveillance: 62.9 (9.8) 41.5% NR	Macrogol (2&3 days prior) PEG (on the day and 1 day prior) Sodium picosulphate booster Bisacodyl if required	Same or adjacent colonic segment; size at CCE +/- 50% has to overlap with size on COL +/- 50%
Mahdi 2023[33] England Funding NR	Retrospective, single-centre analysis	NG12 symptoms and FIT 10-100µg/g who were given CCE	76	64 (NR) M:F ratio 1:1.2	NR	NR

Author year Country Funding/CoI	Study design	Inclusion criteria/ Indication	N patients analysed	Mean age (SD) N Female (% female) Ethnicity	Bowel preparation methodology	Polyp matching criteria
NHSE CCE Pilot Study 2024[32, 40, 68, 78] England NHSE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales Pilot Study	Unclear	FIT <10µg/g, persistent symptoms "low risk" group, likely recruited according to NG12 criteria	NR, n=49 as of July 2023, unclear if more recruited subsequently	NR	NR	NR

ACGBPI - Association of Coloproctology of Great Britain and Ireland; BSG - British Society of Gastroenterology; CCE - colon capsule endoscopy; CoI - conflict of interest; COL - colonoscopy; FIT - faecal immunochemical test; F - female; M - male; N - number; NG12 - National Guideline 12; NHSE - National Health Service England; CRC - colorectal cancer; HNPCC - hereditary non-polyposis colorectal cancer; NR - not reported; N/A - not applicable; SD - standard deviation.

**The 3-yearly post-polypectomy surveillance COL pathway is defined by the BSG/PHE/ACPGBI post-polypectomy guidelines as: Five or more premalignant polyps or two or more premalignant polyps including one or more advanced polyp. Advanced polyps are: serrated polyp ≥10mm or serrated polyp with dysplasia*

†Proportions recruited according to indication: Symptomatic: Change in bowel habit 209 (66.1), Abdominal mass 132 (41.8), Rectal bleeding 69 (21.8), Positive FIT 63 (19.9), Diarrhoea 60 (19.0), Constipation 41 (13.0), Weight loss 30 (9.5), Microcytic anaemia 6 (1.9), Other 12 (3.8); Surveillance: Previous polyps with fewer than [sic] polyps on previous COL 100 (51.8), CRC surgery follow-up 35 (18.1), Family history 23 (11.9), HNPCC gene history (without family history of gastric cancer) 11 (5.7), Other 24 (12.4).

Outcomes

Data relating to outcomes are reported Table 14, Table 15 and Table 16.

Test uptake: Only one study reported data on test uptake (see Table 14). In this study, 96 patients (13%) refused referral.[31] Reasons for refusals were reported, but more than one reason per patient could be recorded, so it was not possible to add together categories to provide overall proportions. Reasons for subjects refusing the referral related to CCE were noted 47 times, and included preferring COL (n=31), being not interested or not wanting CCE (n=12), and concerns about swallowing the capsule/having it inside them (n=4). Refusal because of the bowel preparation regimen, which may also affect a referral to COL, was noted five times. Other reasons, which may also affect a referral to COL, included having other medical conditions (n=5), having insufficient time (n=4), and being out of the area (n=2). Thirty-eight percent (n=36) did not provide a reason. After agreeing to the referral, a further 68 patients (9%) declined the procedure, and reasons were similar. Reasons related to CCE were noted 16 times, and to bowel preparation, 8 times. Thirty-eight percent gave no reason. Additional patients withdrew from the study, 10 patients could not swallow the capsule, 8 had problems with bowel preparation, and 6 had a blacklist condition. Across declinations and withdrawals at all stages, reasons attributable to CCE were noted 73 times, but it is unclear how many patients this relates to overall. Reasons related to bowel preparation were cited a further 17 times.

Bowel preparation: A description of the bowel preparation regimen was only available for ScotCap,[31] where PEG, sodium picosulphate and bisacodyl were used (see Table 13). Adequate bowel preparation ranged from 62%[33] to potentially as high as 91.5%,[40] although this latter value was calculated from 8.5% reported as *"incomplete due to inadequate bowel preparation"* and it is unclear if some patients whose CCE was incomplete for other reasons may also have had inadequate bowel preparation.

Completion rates, retention, AEs and technical failures: Data are reported in Table 15. Three studies[31, 34, 40] reported completion rates which ranged from 69%[34] to 72%.[31] Two studies reported retention rates which were 0.2%[31] and [redacted][40] Other CCE complications were reported by [redacted], whilst the ScotCap study[31] reported inability to swallow (1.6%), dehydration (0.2%), problems with bowel preparation (1.3%), Mallory-Weiss tear from vomiting (0.2%) and technical failure (0.3%). Two studies[33, 34] provided little or no data on retentions, AEs and technical failures.

Table 14: Data on test uptake

Author year Country Funding/CoI	No response to referral n/N (%)	Declined referral to CCE n/N (%)	Declined CCE after agreeing to CCE n/N (%)	Withdrawal from study n/N (%)
MacLeod 2022[31] Scotland Scottish Government	36/733 (5%)	**Declined CCE referral: 96/733 (13%)** **Related to CCE*** Prefer COL 31 (32.3) Not interested/does not want CCE 12 (12.5) Concerns about swallowing capsule/having capsule inside them 4 (4.2) **Related to bowel prep*** Bowel prep (can't tolerate, doesn't want it) 5 (5.2) **Other reasons*** No reason given 36 (37.5) Other medical conditions 5 (5.2) Time commitments (time off work, unable to do at present) 4 (4.2) On advice 3 (3.1) Out of area 2 (2.1) Does not want CCE or COL 2 (2.1) Travel 1 (1.0) Other reasons 3 (3.1)	**Declined after agreeing to the CCE referral: 68/733* (9%)** **Related to CCE*** Prefer COL 9 (13.2) Concerns about swallowing capsule/having capsule inside them 6 (8.8) Not interested/does not want CCE 1 (1.5) **Related to bowel prep*** Bowel prep (can't tolerate, doesn't want it) 4 (5.9) **Other reasons*** No reason given 26 (38.2) Other medical conditions 8 (11.8) Time commitments (time off work, unable to do at present) 7 (10.3) End of evaluation 6 (8.8) Travel 4 (5.9) COVID-19 2 (2.9) Does not want CCE or COL 2 (2.9) On advice 1 (1.5) Out of area 1 (1.5)	**Withdrew during study: 24 (3%)** **Related to CCE*** Patient could not swallow: 10/733 (1%) **Related to bowel prep*** Problems with bowel prep (CCE not swallowed): 8/733 (1%) **Other reasons*** Blacklist condition: 6/733 (0.8%)
Mahdi 2023[33] England Funding NR	NR	NR	NR	NR
NHSE study[32, 40, 68, 78] England NHSE	NR	NR	NR	NR
Wales Pilot study	NR	NR	NR	NR

CCE - colon capsule endoscopy; COL - colonoscopy; NHSE - National Health Service England; CoI - conflict of interest; NR - not reported
** Can be more than one reason across all categories. Therefore, total proportions cannot be calculated.*

Table 15: **Diagnostic yield, bowel cleansing, completion rates and adverse events for studies in scope-defined populations**

Author year **Country** **Funding/CoI** **Definition of polyp outcome**	**Inclusion criteria (% in scope)** **N analysed**	**Bowel cleansing level, n/N (%)**	**Completion rates n/N (%)** **Excretion & retention rates** **AEs** **Tech failure**	**N Polyps <6mm (%)**	**N Polyps 6mm - 9mm (%)**	**N Polyps <10mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)**	**N other bowel pathology (%)** **N no other bowel pathology (%)**
MacLeod 2022[31] (ScotCap) Scotland Scottish Government Unclear, possibly TPs only for those selected for further tests/ interventions	1. Symptomatic referred from primary care 316	79%	**Symptomatic:** 228/316 (72%) **Surveillance:** 137/193 (71%) **For 1&2** ***Retention:*** 1/601 (0.2) ***AEs:*** Could not swallow: 10/601 (1.6) Dehydration: 1/601 (0.2) Bowel prep issues: 8/601 (1.3) Mallory-Weiss tear: 1/601 (0.2) ***Tech failure:*** 2/601 (0.3)[†]	≤6mm: 34 (11%)	7-9mm: 33 (10%)[*]	NR, calculated as 21%	≥10mm: 22 (7%)[*]	0 (0.0)	IBD: 10 (5.2) Diverticular diseased: 1 (0.5)

Author year **Country** **Funding/CoI** **Definition of polyp outcome**	**Inclusion criteria (% in scope)** **N analysed**	**Bowel cleansing level, n/N (%)**	**Completion rates n/N (%)** **Excretion & retention rates** **AEs** **Tech failure**	**N Polyps <6mm (%)**	**N Polyps 6mm - 9mm (%)**	**N Polyps <10mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)**	**N other bowel pathology (%)** **N no other bowel pathology (%)**
	2. Surveillance for personal/ family history CRC; history of colonic polyposis; hereditary nonpolyposis CRC 193	66%		≤6mm: 38 (20)	7–9mm: 13 (7)	NR, calculated as 26%	≥10mm: 9 (5.0)	CRC: 0 (0.0)	IBD: 0 (0.0) Diverticular diseased: 0 (0.0)
Mahdi 2023[33] England Funding NR CCE-detected pathologies (TP+FP)	NG12 symptomatic with FIT 10-100µg/g 76	29/76 (38%) poor preparation	NR NR NR NR	23 polyps (30%) 19 had further endoscopy: low-grade dysplasia or hyperplastic, size range 2-8mm in 18; 1 sigmoid malignancy.				1	10 diverticular disease (13) 1 IBD (1) 4 “other pathologies” (5)
NHSE CCE Pilot Study[32, 40, 68, 78]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Author year **Country** **Funding/CoI** **Definition of polyp outcome**	**Inclusion criteria (% in scope)** **N analysed**	**Bowel cleansing level, n/N (%)**	**Completion rates n/N (%)** **Excretion & retention rates** **AEs** **Tech failure**	**N Polyps <6mm (%)**	**N Polyps 6mm - 9mm (%)**	**N Polyps <10mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)**	**N other bowel pathology (%)** **N no other bowel pathology (%)**
England NHSE CCE-detected pathologies (TP+FP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wales pilot study[34] Wales Funding NR Definition NR	Symptomatic with FIT <10µg/g NR	86%	69% NR NR NR	57% significant bowel disease detected (IBD/ polyps/cancer/diverticular disease/haemorrhoids)					

AE - adverse event; CCE - colon capsule endoscopy; CD - Crohn's disease; CRC - colorectal cancer; FIT - faecal immunochemical test; IBD - inflammatory bowel disease; n or N - number; NG12 - National Guideline 12; NHSE - National Health Service England; NR - not reported; UC - ulcerative colitis

** Sensitivity for detection of polyps amongst those who had an endoscopy after CCE: per polyp analysis: ≥6mm, 91% (95% CI 86.3–93.9); ≥10mm 95.2% (95% CI 89.1–98.4); per patient analysis: ≥6mm, 89.9% (95% CI 83.1–94.7); ≥10mm 93.8% (95% CI 84.4–98.3)*

† Technical failure of recorder:1 data recorder misplaced, CTC given instead: 1.

Identification of polyps and other colonic diseases: Data are reported in Table 15. Data were not reported for consistent categories across studies, nor were outcomes defined in the same way. For the ScotCap study,[31] it was unclear to the EAG if the number of polyps, IBD and CRC cases reported relate to the number of patients whose disease was confirmed by subsequent tests (TPs), or the number identified by CCE (TPs+FPs). For the NHSE CCE Pilot Study[40] and for Mahdi *et al.*,[33] the available data reflect the number identified by CCE, but not confirmed by subsequent tests (TPs+FPs). For the Wales Pilot Study, it was unclear whether the numbers were confirmed by subsequent tests, or CCE-detected. The NHSE CCE Pilot Study[40] reported data per-patient for polyps <10mm, ≥10mm, CRC and IBD; this breakdown was requested to inform the EAG's economic model. Data relating to the confirmation by subsequent tests (COL or FSIG) were also obtained for use in the model (see Section 4.3). ScotCap[31] reported data per-patient for polyps ≤6mm, 7-9mm, ≥10mm, CRC, IBD and diverticular disease. The Wales Pilot[34] only reported data for all disease grouped together (IBD/polyps/cancer/diverticular disease/haemorrhoids) and Mahdi *et al*.[33] reported data for all polyps, CRC, IBD, diverticular disease and "other pathologies" separately.

In the NHSE CCE Pilot Study,[40] [redacted] In the ScotCap[31] symptomatic population, the number of patients with polyps <10mm was calculated by the EAG as 21% (the sum of data for ≤6mm and 7-9mm), the number with polyps ≥10mm was reported as 7%, there were no CRC cases and 5% had IBD. The study by Mahdi *et al*.[33] appears to also have lower prevalence of polyps overall (any size, 30%) compared to the NHSE CCE Pilot Study, even though it reported TP+FP. The Wales Pilot Study[34] did not report data per outcome, but reported that 57% of patients had any significant bowel disease. The EAG noted differences in prevalence between the studies (the NHSE Pilot Study generally had higher prevalence compared to ScotCap[31] and Mahdi *et al*.[33]) but was unsure why.

Subsequent tests after CCE: All four studies reported data on subsequent tests or discharge. These data are reported in Table 16, except for the Wales Pilot Study, as the data were reported in a different format. Additional "capacity spared" diagrams were provided by the NHSE CCE Pilot Study Investigators through personal communication and these are reproduced in Appendix 6, Figure 12, Figure 13 and Figure 14. No further luminal investigations were required for symptomatic patients with [redacted] and 50%[33] (50% calculated, see Table 16) and [redacted]. For symptomatic patients referred in Scotland, 37%[31] of cases required no further tests. In the Wales Pilot Study,[34] 36% of patients were reported to need "further investigation" but the nature of the investigation was not clear. A further

21% of patients were discharged to their GP, 17% back to the referrer or secondary care and 12% were followed up in clinic. For the NHSE CCE Pilot Study surveillance population,[40] the proportion who had no further luminal investigation was [redacted] than for the symptomatic population in the same study at [redacted]. The types of subsequent tests are reported in Table 16. Across surveillance and symptomatic populations, after CCE, COL was used in between [redacted][40] and 54%[31] of patients, FSIG in between 7%[33] and 26%,[31] CTC in between [redacted] and 3%[31] and a second CCE in [redacted]There were also small proportions of patients scheduled for later follow-up or whose follow-up had not yet occurred (see Table 16).

Table 16: Numbers and proportions of subsequent tests after CCE

	NHSE CCE Pilot Study[32, 40, 68, 78]	MacLeod 2022 (ScotCap)[31]		Mahdi 2023[33]
Subsequent test	[redacted]	**Symptomatic N=316**	**Surveillance N=193**	**Symptomatic FIT 10-100µg/g N=76**
Subsequent colorectal investigations	[redacted]	**198 (63%)**	**53 (27%)**	
Urgent (within 28 days)	[redacted]	NR	NR	NR
• COL	[redacted]	NR	NR	NR
• FSIG	[redacted]	NR	NR	NR
• CTC	[redacted]	NR	NR	NR
• CCE	[redacted]	NR	NR	NR
Non-urgent (>28 days post CCE)	[redacted]	NR	NR	NR
• COL	[redacted]	NR	NR	NR
• FSIG	[redacted]	NR	NR	NR
• CTC	[redacted]	NR	NR	NR
• CCE	[redacted]	NR	NR	NR
Total Urgent + non-urgent				

	NHSE CCE Pilot Study[32, 40, 68, 78]	MacLeod 2022 (ScotCap)[31]		Mahdi 2023[33]
Subsequent test		**Symptomatic N=316**	**Surveillance N=193**	**Symptomatic FIT 10-100µg/g N=76**
• COL		103 (33%)	104 (54%)	31 (41)¶
• FSIG		81 (26%)	30 (16)	5 (7)¶
• CTC		9 (3%)	4 (2%)	1 (1)¶
• CCE		0 (0%)	0 (0%)	0 (0)
• Other		5 (2%)	2 (1%)	1 (1)¶
Future planned colorectal investigations		**NR**	**NR**	**NR**
• 3-year surveillance		NR	NR	NR
• 1 year surveillance		NR	NR	NR
• Not completed prior to end of study		NR	NR	NR
Not specified		NR	NR	NR

	NHSE CCE Pilot Study[32, 40, 68, 78]					MacLeod 2022 (ScotCap)[31]		Mahdi 2023[33]
Subsequent test	[redacted]					**Symptomatic N=316**	**Surveillance N=193**	**Symptomatic FIT 10-100µg/g N=76**
No further colorectal investigations	[redacted]					**118 (37%)**	**53 (27%)**	**NR, calculated as 38/76 (50%)**
• Discharged	[redacted]					NR	NR	NR
• Declined/unfit	[redacted]					NR	NR	NR
• Other GI investigations	[redacted]					NR	NR	NR
• Lost to follow-up	[redacted]					NR	NR	NR

CCE - colon capsule endoscopy; CD - Crohn's disease; COL - colonoscopy; FSIG - flexible sigmoidoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; GI - gastrointestinal; n or N - number; NHSE - National Health Service England; NR - not reported.

[redacted]

§ Reported in the source document[40] as 74%, which appears to be a proportion of the total number of patients. We have reported 71% as a proportion of the total number of CCE tests reported in the dataset (3631 + 998 + 464 = 5093).

¶ *COL: comprises 15 COLs conducted in patients whose CCE was non-diagnostic due to poor preparation, 15 COLs done after finding polyps on CCE, and one assumed to have been done for the one patient with cancer; FSIG: comprises 2 done in patients whose CCE was non-diagnostic due to poor preparation, and one done after finding polyps on CCE; CTC and "other" (plain abdominal CT) both done in patients whose CCE was non-diagnostic due to poor preparation.*

3.3.3.2 Studies in patients with incomplete COL or who refused COL

No studies met the initial criteria relating to patients with incomplete COL or who refused COL. The inclusion criteria were widened (Widened 3, see Table 2) to: (a) include studies which recruited more than 50% patients who were symptomatic or undergoing polyp surveillance as per the final NICE scope[35] and (b) include studies that reported diagnostic yield rather than diagnostic test accuracy. Consequently, seven studies were included.[53, 56, 58, 62, 72, 73, 76]

Six additional studies[52, 55, 59, 65, 79, 84] were excluded from this analysis for the following reasons: the reasons for the initial referral to COL were not reported;[79] there was a lack of clarity about whether FOBT was used in symptomatic or screening populations and therefore whether the patients were within the scope of the appraisal;[65] it was unclear if PillCam COLON 2 was used, even after attempts to contact the author were made;[52] >50% of the patients were out of scope.[55, 59, 84] Sensitivity analyses to include these studies were not performed due to time constraints and the low value such analyses would have given the inherent limitations of diagnostic yield studies (i.e., they do not report diagnostic test accuracy).

Study characteristics: The characteristics of the included studies are provided in Table 17. All were prospective cohort studies conducted in Europe, but none were undertaken in England or the UK. The sample sizes analysed ranged from 50[76] to 689 patients,[56] with all but one[56] being below 100. None reported only symptomatic or polyp surveillance patients, with the proportion in-scope ranging from 52%[58] to 74%,[76] with one study unclear, but >50%.[72] Five studies[53, 58, 62, 73, 76] recruited only those who had an incomplete COL, whilst two[56, 72] recruited both those with incomplete COL and those who refused COL. In all but two studies[56, 58] patients with inadequate bowel preparation were excluded (see footnotes to Table 17).

Table 17: Studies in patients with incomplete COL, or who refused COL

Author year **Country** **Funding/ CoI**	**Incomplete, declined or both?** **Study design**	**Indication for initial COL (% in scope)**	**Bowel cleansing level, n/N (%)**	**N recruited, N analysed**	**N Polyps <6mm (%)**	**N Polyps 6mm-9mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)** **N other bowel pathology (%)**	**Completion rate (%)**[¶¶] **Completed COL rate (%)**[¶¶] **Excretion & retention rates** **AEs**	**Follow-up COL/ other, n (%)**
Studies with confirmatory COL										
Spada 2015[62] Italy Some authors consultants for Given Imaging	Incomplete[*] Prospective cohort	Symptoms, polyp surveillance, CRC screening, family history, FOBT+ (62)	Adequate n NR (83)	100 97[‡]	NR	NR for 6-9mm ≥6mm: 25 (26) Col confirmed: 24/25 (96)	6 (6) COL confirmed: 5/6 (83)	NR NR	• Completion: NR • Completed COL: 98/100 (98) • Excretion w/in 10 hrs: 93/100 (93) • Retention: 1, but unclear for how long • AEs related to bowel prep[§]	COL: 26 (27) (however, this was on the basis of a positive CCE or a positive CTC. 25/97 (26%) on the basis of a positive CCE)
Hussey 2018[76] Ireland Medtronic provided capsules	Incomplete[*] Prospective cohort	Symptoms, polyp surveillance, family history, IBD assessment, abnormal imaging (74)	Poor preparation 4/50 (8) (equates to 46/50 (92) with adequate preparation)	50 50	Any polyp: 19 (38) Significant polyp[†]: 7 (36) Per-polyp findings: - Tubulovillous adenoma with low-grade dysplasia 8 (57) - Tubulovillous adenoma with high-grade dysplasia 1 (7) - Sessile-serrated adenoma 2 (14) - Hyperplastic polyps 3 (21) COL confirmed polyps in 7/7 patients referred for COL			CRC: 0 (1 small bowel neuro-endocrine cancer found incidentally) Other: Inflammation (22) Diverticular disease (25) Angiodysplasia (3) Small bowel Crohn's disease (4)	• Completion: 38/50 (76) • Completed COL: 42/50 (84) • Excretion: 49/50 (98) • Retention: 1 (2) • Abdominal pain: 2 (4)	Polypectomy: 7 (14) Surgery to remove capsule: 1 (2) IBD therapy escalation 4 (8) Cauterisation of angiodysplasia 1 (2)

Author year **Country** **Funding/ CoI**	**Incomplete, declined or both?** **Study design**	**Indication for initial COL (% in scope)**	**Bowel cleansing level, n/N (%)**	**N recruited, N analysed**	**N Polyps <6mm (%)**	**N Polyps 6mm-9mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)** **N other bowel pathology (%)**	**Completion rate (%)**[¶] **Completed COL rate (%)**[¶] **Excretion & retention rates** **AEs**	**Follow-up COL/ other, n (%)**
Deding 2020[58] Denmark (Odense) Medtronic provided capsules	Incomplete[*] Prospective paired	Symptoms, screening, surgery follow-up (52)	Adequate N NR (76)	105 97[‡]	NR	NR for 6-9mm >5mm: 40 (41) Col confirmed: 15/25 (60%)	>9mm 21 (22) COL confirmed: 5/18 tested (30%)	NR NR	• Completion: 66/105 (63)[¶] • Completed COL: 73/105 (70) • No AEs occurred	COL as CCE incomplete: 10 (10) Referred to COL overall: 32 (33)
Benech 2021[56] France Study funded by Medtronic	Both* (52.4% in-scope; 44.6% contraindicated for COL) Prospective cohort	Symptoms, family history, screening, other (67)[#]	Adequate 477/689 (69)	1282 689[‡]	Significant polyps (≥6 mm and/or ≥ 3 polyps): 187 (27.1) COL confirmed: 110/228 tested[**] (48) In one case, advanced neoplasia was missed by CCE, whilst 31/32 were identified.			CRC: 32 advance neoplasia, 21 of which were CRC Other: Diverticula (13) Angiodysplasia (2) Ulceration (1) Other (3)	• Completion: 442/689 (64) • Complete with good cleansing 337/689 (49) • Completed COL: NR, but 83/187 (44) identified with significant polyps had incomplete/ inadequate bowel preparation; 409 not recommended COL, of which 124 (30) had incomplete CCEs • Retention and AEs NR	Recommended COL: 280 (41) Recommended but COL not performed: 52 (8) COL not recommended: 409 (59)

Author year **Country** **Funding/ CoI**	**Incomplete, declined or both?** **Study design**	**Indication for initial COL (% in scope)**	**Bowel cleansing level, n/N (%)**	**N recruited, N analysed**	**N Polyps <6mm (%)**	**N Polyps 6mm-9mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)** **N other bowel pathology (%)**	**Completion rate (%)**[¶¶] **Completed COL rate (%)**[¶¶] **Excretion & retention rates** **AEs**	**Follow-up COL/ other, n (%)**
Studies reporting yield with confirmatory procedures other than COL										
Negreanu 2013[72] Romania ESGE-GIVEN[‡‡]	Both[*] Prospective cohort	Symptoms, family or personal history of polyps or cancer, other screening, abnormal imaging or markers (≥50%)[§§]	48/70 (69)	70 67	≤6mm 6 (9)	Polyp >6 mm 5 (7) ≥3 polyps 10 (15) Significant polyps (>6mm or ≥3 polyps) 15 (21)		CRC: 4 (6) Other: Multiple colonic angiomas 2 (3) Other digestive cancers 2 (3) CD 1 (1) UC 1 (1) Radiation enteritis 1 (1) Diverticulosis 17 (25)	• Completion: 54/70 (77) • Completed COL: 63/70 (90) • Excretion w/in 12 hrs: 54/70 (77), w/in 48 hrs: 68/70 (97) • Retention: 2/70 (3) • AE's: None observed	17 out of the 23 with relevant lesions diagnosed by CCE agreed to have a therapeutic intervention 17/67 (25)
[72]**Studies reporting yield only with no data from confirmatory COL**										
Baltes 2018[73] Germany Given Imaging funded work/paid lecture fees	Incomplete* Prospective cohort	Symptoms, CRC screening, colitis, B Symptoms (lymphoma) and "other" (54)	Adequate 53/81 (65)	81 74[‡]	3 (4)	10 (14)	8 (11)	CRC: Adenocarcinoma 1 (1) Other: Angiectasia 3 (4) Diverticulitis 1 (1) Small bowel CD 1 (1)	• Completion: 48/74 (65) • Completed COL: 72/81 (89) • Excretion w/in 7 hrs: 29/74 (39) • Retention: 1 (1) • Nausea: 1(1)	Further diagnosis or treatment 18 (22)

Author year **Country** **Funding/ CoI**	**Incomplete, declined or both?** **Study design**	**Indication for initial COL (% in scope)**	**Bowel cleansing level, n/N (%)**	**N recruited, N analysed**	**N Polyps <6mm (%)**	**N Polyps 6mm-9mm (%)**	**N Polyps ≥10mm (%)**	**N CRC (%)** **N other bowel pathology (%)**	**Completion rate (%)⁋** **Completed COL rate (%)⁋** **Excretion & retention rates** **AEs**	**Follow-up COL/ other, n (%)**
Havshoi 2023[53] Denmark (Nyborg) Declared no CoI	Incomplete* Prospective cohort	Symptoms, surveillance, screening (unclear if all surveillance was for polyps, therefore 61)	Adequate 34/63 (54)	NR 63	≤5mm 3 (5)	>5mm 35 (56)	>9mm 13 (21)	NR NR	• Completion: 25/63 (40)†† • Complete transit 38/63 (60)†† • Completed COL: NR • Excretion/ retention: NR • No AEs occurred	COL under anaesthetic: 44/63 (70) CTC: 4/63 (6)
					COL confirmed: 24/37 CCE positive patients tested (65)					

CCE - colon capsule endoscopy (PillCam COLON 2); CoI - conflicts of interest; COL - colonoscopy; CRC - colorectal cancer; UC - ulcerative colitis; CD - Crohn's disease; CTC - computed tomography colonography; FOBT+ - faecal occult blood test positive; hrs - hours; N - number; w/in - within

** **Hussey et al., 2018** excluded patient with incomplete COL due to obstruction or inadequate bowel preparation; **Baltes et al., 2018** only included patients with incomplete COL due to a failure to reach the cecum or ileo-cecal anastomosis due to looping, bowel angulation, adhesions, and intolerance of sedation or inflammation; **Spada et al., 2015** excluded patients if their COL was incomplete due to inadequate preparation and/or the presence of colonic strictures; **Deding et al., 2020** exclusion criteria were previous gastrointestinal surgery (except for appendectomy), known inflammatory bowel disease, ostomy, diabetes, symptoms of bowel obstruction, pacemaker and/or severe kidney disease. No patients were excluded because of noncompliance to bowel preparation, constipation or history of poor bowel preparation. **Benech et al., 2021** included patients with COL contraindications (44.6%), incomplete COL (31.5%), patient refusal (20.9%) and other reasons (3%), this could include insufficient bowel preparation (see Table 4 in Benech et al.,); **Havshoi et al., 2023** excluded patients with poor bowel preparation at incomplete COL, stenosis, previous colonic resection, ostomy, inflammatory bowel disease, dysphagia, dysregulated diabetes, kidney dysfunction, pacemaker, pregnancy or waist measure > 140 cm*

*† **Hussey et al., 2018** significant polyps defined as polyp>6mm or ≥3polyps*

*‡patients not in analysis: **Negreanu et al., 2013** refusal of a COL in 37 patients, previous incomplete COL (mostly technical failures of initial COL) in 30 patients or unable to perform COL (the examination risks-cardiovascular or anesthetic were considered excessive by their own physicians) in 3 patients; **Baltes et al., 2018,** technical failure (n = 1), protocol noncompliance as a result of incorrect timing of CCE (n = 4), exchange of colonoscope (n = 1) or early removal of recorder by the patient (n = 1); **Spada et al., 2015**, compared CCE to CTC, patients had to complete both - 2 refused CTC, 1 didn't excrete CCE, therefore couldn't complete CTC; **Deding et al., 2020,** 8 withdrew consent; **Benech 2021 et al.,** this was a retrospective study of routine practice, 593 did not have a complete CCE or COL report available. § nausea (n=11), vomiting (n=7), headache (n=6), abdominal pain (n=3) and vertigo (n=1).*

⁋ completion was defined as capsule excretion within recording time and bowel cleanliness was graded as 2–4 by the Leighton–Rex Scale (no reference provided). The authors noted that if the definition of complete was when the hemorrhoidal plexus was visualized, completion rate may have been higher, but do not give numbers.

*# 67% were referred for original COL for reasons in line with the NICE scope. However, whilst 52.4% of the patients recruited to the study had incomplete COL or refused COL, it is unclear how many of the 67% with in-scope referrals ** 228 COLs were recommended, some for reasons other than polyps, e.g., insufficient bowel cleansing, persistent symptoms*

†† Complete investigation was at least a fair level of bowel preparation in each colonic segment and visual of anal valve; Complete transit was visual of the anal valve.

‡‡ ESGE not defined in this context, but may be European Society of Gastrointestinal Endoscopy. Unclear if GIVEN indicates industry funding from Given Imaging.

§§ 35/70 patients had symptoms, 5/70 being followed up for personal history of polyps or cancer. ⁋⁋ Completion rate was defined as full visualisation of the colon, i.e., the capsule was excreted with the battery still functioning. Completed COL rate was defined as CCE procedures that reached the most proximal site of the incomplete COL

Metrics reported: All seven studies reported diagnostic yield as the number of positive CCE tests (i.e., TP+FP). Four studies[53, 58, 62, 76] also reported the number of CCE-positive patients, and the results of any COL investigations that followed. These studies were therefore able to determine TPs and FPs amongst CCE-positive patients. However, most patients without a positive finding were not followed up with COL, so FNs were not ascertained, and sensitivity and specificity could not be calculated. It could be argued that CTC and CCE with COL-confirmation in those with a positive CCE or CTC could create a composite reference standard, since CCE and CTC should identify most cases. This applies to Spada *et al.*, 2015,[62] though it should be noted that the authors do not present this study as a diagnostic test accuracy study. The EAG considered this potential reference standard carefully, but take the view that the reference standard would be at high risk of partial verification bias[85] since some patients receive no reference standard (or only telephone follow-up for CRC cases), at high risk of conditional dependence bias[86] since the type of reference standard test given is determined by the index test, at high risk of bias due to the low specificity of the component tests meaning the reference standard is likely to create FPs compared to actual disease status,[86] and high risk of incorporation bias[87, 88] since one of the components is also one of the index tests. Therefore, sensitivity and specificity have not been calculated for this study.

Two of these included studies[58, 62] also reported data for CTC in the same patients, and calculated "relative sensitivity", which is a ratio of the TPs determined by each test, since the denominator in the calculation for sensitivity (TPs plus FNs) would be the same for each test, thereby negating the need to ascertain FNs to perform the calculation. However, in one study,[58] it appears that what has been calculated is in fact "relative diagnostic yield", i.e., the ratio of the number of CCE-positive patients and CTC-positive patients, probably because not all patients with findings were given a COL (see Table 17).

One further study[76] performed COL on patients with a positive CCE, but reported results per patient for positive CCEs, but per polyp for COL confirmation.

One study[72] reported the findings on CCE, and for those with "relevant lesions" the proportion who went on to have a "therapeutic intervention" (e.g., surgery, COL) which could confirm the CCE finding. However, the data reported were insufficiently clear for data extraction to be performed and are not discussed further.

The remaining one included study[73] did not report whether the findings in CCE-positive patients were confirmed with COL and therefore report diagnostic yield only.

Five studies[58, 62, 72, 73, 76] reported data on CCEs that completed COLs, i.e., that reached the most proximal site of the incomplete COL.

Summary of results: Data are reported in Table 17. Adequate bowel cleansing levels ranged from 54%[56] to 92%.[76] Completion rates ranged from 40%[53] to 77%.[72] When including CCEs that completed incomplete COLs (see Section 3.1.1.4) in the completion rate, it ranged from 70%[58] to 98%.[62] Four studies reported retention of one or more capsules,[62, 72, 73, 76] whilst two[53, 58] reported no AEs and one did not mention AEs.[56] Other AEs included nausea,[62, 73] vomiting,[62] headache,[62] vertigo[62] and abdominal pain.[76, 62]

Subsequent to CCE, the proportion of patients who were referred for subsequent procedures (COL, surgery, polypectomy, CTC or other unspecified therapies) ranged from 22%[73] to 76%,[53] and specifically for COL from 26%[62] to 70%.[53]

Diagnostic yields for polyps <6mm,[72] ≤5mm[52] and ≤6mm[71] (the EAG was unsure if <6mm and ≤5mm equate to the same category, e.g., if polyp size is rounded to the nearest whole number) were reported in three studies[53, 72, 73] and were 4%[73], 5%[53] and 9%,[72] respectively. Diagnostic yields could be worked out for polyps sized 6-9mm for two studies[53, 73] and were 14%[73] and 56%.[53] Diagnostic yield for polyps >9mm was reported in two studies[53, 58] and ≥10mm in two studies[62, 73] (the EAG was unsure if these categories equate to the same category, e.g., if polyp size is rounded to the nearest whole number) and ranged from 6%[62] to 22%.[58 53, 73] Two studies reported diagnostic yield for significant polyps, defined as polyps ≥6 mm and/or ≥ 3 polyps, with values of 27%[56] and 36%,[76] respectively. Two studies[58, 62] reported diagnostic yield for polyps ≥6mm, which were 26%[62] and 41%.[58] One study[72] reported diagnostic yield for polyps >6mm (rather than ≥6mm) and this was 7%, and for significant polyps defined as >6mm and/or ≥ 3 polyps and this was 21%.

COL confirmation (i.e., distinguishing between TPs and FPs) of polyps was reported in four studies, but most had limitations. In one study,[58] patients with polyps were not automatically sent for COL, but were further selected based on clinical opinion, thereby potentially enriching the sample with TPs. However, conversely, in comparison to a study where all patients with positive findings on CCE were sent for COL,[62] the confirmation rates were actually lower: for polyps ≥6mm and ≥10mm, respectively, 96% and 83% were confirmed where all patients were given COL,[62] whereas 60% and 30% were confirmed where patients were further selected by a clinician.[58] In the two other studies, both reported "significant polyps" only; in one,[76] all 7 patients with significant polyps on CCE were confirmed (see Table 17), whilst the other[56] reported that 48% of significant polyps were confirmed by COL.

The study that reported relative sensitivity between CCE and CTC reported a value of 2.0 (95% CI 1.34 to 2.98) for polyps ≥6mm, and 1.67 (95% CI 0.69 to 4.00) for polyps ≥10mm. The study that reported what the EAG believes to be relative diagnostic yield between CCE and CTC reported a value of 2.67 (95% CI 1.76 to 4.04) for polyps ≥6mm, and 1.91 (95%CI 1.18 to 3.09) for polyps ≥10mm.

3.3.4 Patient preference studies

This section summarises the identified evidence relating to patient preference. For patient preference studies, it was not necessary to widen the criteria for symptomatic patients, since some studies were available that met the original criteria. However, for surveillance patients, the criteria were widened to include one study[66] that had >50% patients in scope, some of whom were under surveillance for previous polyps ("Widened 4", see Table 2). For the study that was included, it was, however, unclear how many with "previous polyps" met the criteria of "post-polypectomy surveillance COL at 3 years because of high-risk findings at their baseline COL". The reasons for referral may affect patient acceptability, e.g., patients' perceptions of risk of CRC may affect their expectation of the need for a subsequent COL, or the need for an accurate test. For one study, it was unclear whether the test used was PillCam COLON 2 in all patients. The EAG attempted to contact the corresponding author but received no reply. The study is included based on the balance of probability that the test used was PillCam COLON 2, but this uncertainty should be borne in mind.

Following the modification of the inclusion criteria, four studies[34, 45, 66, 71] were included in the analysis of data on patient preference, one from each of Scotland,[66] England,[71] Ireland[45] and Wales.[34] The Scottish study[66] was part of the ScotCap evaluation of CCE in routine use in Scotland[31] reported in Section 3.3.3. The Irish study[45] was part of the diagnostic test accuracy study reported in Section 3.3.2. The Welsh study has not yet reported in full and data were extracted from a grey-literature presentation which was available online.[34]

One study[72] included in Section 3.3.3.2 reported patient preference for patients who had an incomplete COL or who refused COL. This study did not meet the widened inclusion criteria for the patient preference review, and has not been integrated into this section, but is reported here for completeness. All 70 patients accepted CCE, even though they were informed the bowel preparation regimen was more intensive (note: the bowel preparation regimen in the UK may not be more intensive than that for a COL, but the booster regimen is additional). All appreciated the non-invasive nature of CCE and 65/70 (93%) were willing to have their next surveillance examination by CCE.

Study and patient characteristics: Studies are summarised in Table 18. Study designs were varied, including a retrospective single-centre comparative study comparing CCE and COL via telephone interviews,[45] a prospective two-centre study using patient questionnaires and a lay-public study,[71] comparing COL to CTC and CCE (patients assigned to treatment based on clinical judgement) and a service evaluation across three health boards which incorporated a paper-based survey and additional telephone interviews in a subset of patients.[66] This study reported patient views on CCE, with an additional question asking patients to compare CCE to COL, though they may not have had both tests. The design of one study was unclear but involved patient surveys to gather views on CCE.[34] All studies recruited symptomatic patients, and one study (ScotCap) also recruited surveillance patients who, based on data reported in MacLeod *et al*.,[31] included a proportion who were under surveillance for a history of colonic polyposis. It was not possible to extract data for the surveillance population separately. Sample sizes ranged from 40[45] to 342 patients[71] (n=342 split across COL, CTC and CCE groups). Mean age was reported in 2 studies and was 48[45] and 65[66, 71] years, whilst median ages were reported in one study[71] and were 55 years (range 18-88) in the patients who received COL, 71 years (range 32-87) in CTC patients, and 41 years (range not reported) in CCE patients. The percentage who were female ranged from 49%[66] to 71%.[71] One study[34] did not report bowel preparation, but in the three that did, regimens were fairly similar and included diet manipulation, 4L PEG split over two doses, a Phospho-soda (2 studies),[45, 71] gastrografin[71] or sodium picosulphate[66] booster, and a bisacodyl suppository.

Quantitative results were reported in three studies,[45, 66, 71] and one only reported some headline points relating to patient feedback.[34] The ScotCap study[66] also elicited qualitative responses from patients.

Risk of bias assessment using the MMAT tool:[44] A summary of the MMAT scores for the four included studies is shown in Table 19, with detailed ratings on each item in Appendix 4, Table 58. In general, all four studies had a clear research question and collected relevant data. Of the two quantitative studies,[45, 71] both were well-conducted and reported. All design elements of the qualitative study, the Wales CCE Pilot Study, were difficult to assess as information was only available in a poster presentation and slide set that were accessed via a website about the project.[34] For the mixed-method study[66] (i.e., studies which adopt both quantitative and qualitative data collection methods), the main issue related to the sampling strategy (non-random selection) which limited the representativeness of the findings to the target population. In addition, due to poor reporting, it was unclear whether appropriate approaches were undertaken to collect and analyse the data (e.g. appropriate measurements, non-response bias and statistical analysis).

Table 18: Study and patient characteristics of studies reporting patient preference data for CCE in symptomatic and surveillance populations

Author year Country Funding/CoI	Study design Data collection methods Date of recruitment/study	Inclusion criteria	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	% in scope Indications for referral %	Bowel preparation methodology	Time between procedures
Symptomatic patients							
Ojidu 2018[71] England 1 of 7 authors was a consultant to Medtronic, 6 of 7 authors declared no conflicts	Prospective two-centre study Patient questionnaires May to September 2016	Symptomatic patients Some of CTC and CCE patients had refused or failed COL	COL: 158 CTC: 128 CCE: 56	COL: Mean NR, median 55 (range 18-88); 56% female CTC: Mean NR, median 71 (range 32-87); 63% female CCE: 41 (NR); 71% female NR	100 Symptoms	**COL** Low fibre diet 5 days PEG 2L + 2L Sedation if preferred **CTC** Gastrografin (oral); Hyoscine butylbromide (IV); Contrast (IV) **CCE** PEG 2L + 2L Phospho-soda or gastrografin Bisacodyl	NR
Ismail 2022[45] Ireland No CoI to declare	Retrospective single-centre comparative study Telephone interviews Dec 2017–Dec 2018	Symptomatic patients who had both CCE and COL as part of another study (Ismail 2021,[57] see Section 3.3.2)	40 40	48 (24-78)* 58% female NR	100 Symptoms	**CCE** Diet manipulation "several days" PEG 4L split dose Phospho-soda Bisacodyl **COL** A second PEG 2L+ 2LN	On average 6 weeks (range 2-8 weeks)

Author year Country Funding/CoI	Study design Data collection methods Date of recruitment/study	Inclusion criteria	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	% in scope Indications for referral %	Bowel preparation methodology	Time between procedures
	Prospective lay public choice based on hypothetical situations.[†] Approached in car park of shopping centre with a health centre and pharmacy June 2016	Lay public	100	Mean NR, median 42.5 (range 19–92) 62 NR	N/A	N/A	N/A
Wales pilot study[34] **Wales** **NR**	Unclear NR July 2023	FIT <10µg/g, persistent symptoms "low risk" group	NR, n=49 as of July 2023, unclear if more recruited subsequently NR	NR	NR	NR	NR
Symptomatic and surveillance patients							
Bond 2023[66] **Scotland** **Scottish Government**	Mixed methods service evaluation of patient experience across 3 health boards Survey – paper-based and semi-structured interview via telephone June-December 2019	(1) Symptomatic patients (2) Patients who had symptoms in the past and are under surveillance **For both groups:** Age of 18 years or over, ability to speak and read English, ability to provide consent for the CCE procedure,	317 patients received CCE and 211 completed survey (67%)[§]. However, demographic data only available for 183 patients 1) 101 2) 82	Demographic data: n=183. 64.8 (SD NR, range 34-83) 49 NR	1) 100[¶] 2) 49/82 (60)	Data from MacLeod 2022[31] Macrogol (2&3 days prior) PEG (on the day and 1 day prior) Sodium picosulphate booster Bisacodyl if required	N/A (non-comparative)

Author year Country Funding/CoI	Study design Data collection methods Date of recruitment/study	Inclusion criteria	N recruited N patients analysed	Mean age (SD) N Female (% female) Ethnicity	% in scope Indications for referral %	Bowel preparation methodology	Time between procedures
		and identification as a symptomatic patient. All patients offered survey, and the option to give service evaluation interview, from which an opportunistic sample of 18 participants was selected.‡					

CCE - colon capsule endoscopy; COL - colonoscopy; Dec - December; FIT - faecal immunochemical test; PEG - polyethylene glycol; CoI - conflict of interest; N - number; N/A - not applicable; NR not reported; SD - standard deviation; NR - not reported; N/A - not applicable

** It was unclear what the data in brackets related to, e.g., range, 95% CI*

†Descriptions of procedures, including advantages and disadvantages, which had been approved by Sheffield Bowel Cancer Support Group; assumption that tests had similar test accuracy; information regarding tolerance from the first part of the study; COL information included optional sedation, the taking of biopsies, polypectomies and ability to provide immediate diagnostic information, a non-completion rate 5-10%, perforation or bleeding rate 1:3000 and diagnostic yield 10%; CTC information included the detection of luminal and extraluminal pathology (serious and benign) that might need additional investigation with COL, risk of radiation exposure (responsible for up to 2% of all cancers, personal risk 1:1000); CCE information included a 10% incompletion rate, and possible need for further investigation with COL.

‡ Opportunistic sampling method: contacted each person who opted in until 18 accepted. Originally aimed to recruit 30 but delays to implementation meant only 18 were recruited before the study end.

§ 317 patients received CCE during the evaluation period of the study

⁋ Referral criteria in Scotland differ from England, so the patient spectrum may be different.

Table 19: Quality assessment of the included studies using the Mixed Methods Appraisal Tool (MMAT)

Reference	All studies		1. Qualitative*					2. Quantitative randomised control trials†					3. Quantitative non-randomised‡					4. Quantitative descriptive§					5. Mixed methods ⁋				
	S1	S2	1.1	1.2	1.3	1.4	1.5	2.1	2.2	2.3	2.4	2.5	3.1	3.2	3.3	3.4	3.5	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3	5.4	5.5
Ojidu 2018[71]	Y	Y																Y	Y	Y	Y	Y					
Ismail 2022[45]	Y	Y																Y	Y	Y	Y	Y					
Bond 2023[66]	Y	Y	Y	Y	Y	Y	Y											N	?	?	?	?	Y	Y	Y	Y	N
Wales pilot study[34]	Y	Y	?	?	?	?	?																				

Y - Yes; N - No; ? - Unclear/can't tell

Screening questions (for all types) S1. Are there clear research questions? S2. Do the collected data allow to address the research questions?
* 1. Qualitative. 1.1. Is the qualitative approach appropriate to answer the research question? 1.2. Are the qualitative data collection methods adequate to address the research question? 1.3. Are the findings adequately derived from the data? 1.4. Is the interpretation of results sufficiently substantiated by data? 1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?
† 2. Quantitative randomized controlled trials. 2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?
‡ 3. Quantitative non-randomized. 3.1. Are the participants representative of the target population? 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? 3.3. Are there complete outcome data? 3.4. Are the confounders accounted for in the design and analysis? 3.5. During the study period, is the intervention administered (or exposure occurred) as intended?
§ 4. Quantitative descriptive. 4.1. Is the sampling strategy relevant to address the research question? 4.2. Is the sample representative of the target population? 4.3. Are the measurements appropriate? 4.4. Is the risk of nonresponse bias low? 4.5. Is the statistical analysis appropriate to answer the research question?
⁋ 5. Mixed methods. 5.1. Is there an adequate rationale for using a mixed methods design to address the research question? 5.2. Are the different components of the study effectively integrated to answer the research question? 5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? 5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? 5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Results

The results of both the quantitative and qualitative data have been grouped under 5 headings: satisfaction, dissatisfaction, comfort/discomfort, overall preference and other outcomes. These headings were used in Ismail *et al*.[45] to group data, and were selected by the EAG as suitable categories to base a synthesis around since they covered key aspects of patient preference, and were broad enough to encompass data from all four included studies. The data are summarised in Table 20 and a narrative synthesis provided in the following subsections relating to each category. At the end of each sub-section, a summary of the data is provided.

Satisfaction: All four studies reported on some aspect of satisfaction.

Data comparing CCE to CTC and/or COL: Ismail *et al*.[45] reported satisfaction on a 10-point Likert scale (where higher scores are better) and compared CCE scores to COL scores. Satisfaction was 8.3 (range 3-10) and 7.7 (range 1-10) for CCE and COL, respectively, and the difference between the two was not statistically significant (p=0.2). Ojidu *et al.* reported patient experience on a 0-10 visual analogue scale (VAS) (direction NR, but the EAG assumes that 0 represents "good" and 10 represents "bad" based on the narrative in the journal article) and compared COL, CTC and CCE patients' responses. Values were 5.43, 2.35 and 3.80, respectively; COL was worse than CTC and CCE (p<0.0001), and CTC was better than CCE (p<0.002). The clinical significance of the values was not reported.

Non-comparative data on CCE: The Wales Pilot Study[34] reported that all patients undergoing CCE had a good or very good experience, liked being able to leave the hospital during the procedure, and that they trusted CCE before and more after the procedure. ScotCap[66] reported that 19 patients (denominator NR) found the capsule easier to swallow than expected, that 111/151 patients were satisfied with communication and information, for various reasons including that staff were helpful, friendly, pleasant and reassuring and telephone calls were informative. Similar to the Wales Pilot Study,[34] patients were also satisfied with the impact on daily life in 72 cases, for reasons including less travel, ability to complete the procedure at home, flexibility to do other things, time saved and that they could continue their normal routine.

Summary: Overall, there was general satisfaction with CCE, and some evidence that patients were most satisfied with CTC, but more satisfied with CCE compared to COL. Aspects that patients were satisfied with included convenience, communication and friendly staff.

Dissatisfaction: Three studies[34, 45, 66] reported some data on patient dissatisfaction.

Data comparing CCE to CTC and/or COL: Ismail *et al*.[45] reported the main cause of dissatisfaction was the bowel preparation regimen (25%) for CCE compared to pain and discomfort (33%) for COL. Reasons for dissatisfaction with bowel preparation included the greater volume of liquid and longer time taken compared to preparation for COL.

Non-comparative data on CCE: In the Wales Pilot Study,[34] some patients felt improvements were required to patient information leaflets, in terms of clarity, ease of understanding and the amount of information provided (too much). ScotCap[66] reported on a number of sources of patient dissatisfaction with CCE, based on patient numbers which ranged from three patients to 27 patients (see Table 20 for details). Reasons for dissatisfaction with bowel preparation included the greater volume of liquid and longer time taken compared to preparation for COL (as noted in previous section), and the bad taste. Reasons for dissatisfaction with CCE included pain and discomfort after swallowing the capsule, the prolonged fasting, and the absence of staff during the procedure. Reasons for dissatisfaction with results included having to wait for the CCE results, then having to wait for a COL (where necessary), and results not being clear due to inadequate bowel preparation. Dissatisfaction with information and communication in ScotCap was cited by 46 patients for reasons including inadequate, unclear or overwhelming information on aspects of the test such as risk, misunderstandings about the level of involvement needed for the procedure, and what happens after swallowing the capsule (see Table 20 for details). Dissatisfaction with the impact of CCE on daily life centred around the impact of the need to be near a toilet, and the impact of taking laxatives and of wearing the belt recorder on daily activities and travel.

Summary: Overall, dissatisfaction with CCE centred around aspects of the bowel preparation, pain after swallowing the pill, the wait for CCE results and a subsequent COL where necessary, the impact on daily life of the bowel preparation and wearing the belt, and aspects of patient information.

Comfort/discomfort: All four studies reported on some aspect of comfort with respect to the procedures.

Data comparing CCE to CTC and/or COL: Ismail *et al*.[45] reported comfort on a 10-point Likert scale (where higher scores are better) and compared CCE to COL. Comfort was 9.2 (range 6-10) and 6.7 (range 1-10) for CCE and COL, respectively, and the difference between the two was statistically significant (p=0.0001). Ojidu *et al.*[71] measured comfort using the Gloucester Comfort Score (GCS for pain, 1-5 scale indicating no, minimal, mild, moderate and severe) and compared COL, CTC and CCE. Mean values +/- standard error (SE) for COL, CTC and CCE, were 3.32 ± 0.085, 1.96 ± 0.083 and 1.30 ± 0.088 (p<0.0001), again indicating greater perceived comfort with CCE compared to COL and also to CTC. However, Ojidu *et al.*[71] also reported on nausea, bloating and pain from bowel preparation,

comparing COL, CTC and CCE. CCE had worse values than the other two modalities in all cases (see Table 20 for details) and the differences were statistically significantly different ($p<0.0001$).

Non-comparative data on CCE: Patients in the Wales pilot study[34] noted that the belt and recorder were uncomfortable to wear. In ScotCap, discomfort was noted relating to bowel preparation, the capsule and the recorder and belt. Each reason was cited by ≤15/211 patients (see Table 20 for details). With respect to the bowel preparation, reasons noted included pain and discomfort, feeling unwell and bloated, having longer bowel motions and experiencing bleeding. As noted in "Dissatisfaction" above, discomfort relating to CCE included pain and discomfort after swallowing the capsule and the prolonged fasting. Discomfort relating to the belt and recorder included it being heavy and bulky, uncomfortable and cumbersome, the need for adjustment and restriction of activities.

Summary: Overall, there was some evidence that undergoing a CCE was more comfortable than undergoing a COL or a CTC, but some evidence that there was greater discomfort associated with bowel preparation for CCE, which may be more intensive than bowel preparation for COL. There was some evidence that some patients found that wearing the belt and recorder was uncomfortable and restrictive.

Overall preference: Three studies[45, 66, 71] reported some data on overall preference.

Data comparing CCE to CTC and/or COL: In Ojidu *et al.*,[71] fewer patients who had CCE (86%) would undergo the same test again in the same medical circumstances than patients who had COL (94%), although the difference was not statistically significant. When asked if they would advise a friend to undergo the same test under the same medical circumstances, more patients would recommend COL (96%) than CCE (88%) ($p=0.001$). Comparing CTC to CCE, more CTC patients stated that they would have the same procedure again (96% vs 86%, $p=0.01$), and more would recommend to a friend (100% vs 88%, $p=0.002$). Ojidu *et al.*[71] also elicited preferences from members of the public who were informed about test characteristics (see footnote to Table 18) and asked which test they would prefer if they were symptomatic. For COL, CTC and CCE, the preferences were 45%, 37% and 18% (p=NR).

Non-comparative data on CCE: In Ismail *et al.*,[45] 77.5% of patients (n=31/40) stated that they would choose CCE for a future investigation and 77.4% (the EAG calculates this to equate to n=24/40, 60% of the original sample) of these patients stated that they would still prefer CCE even if a follow-up COL was required after CCE. In the ScotCap study,[66] various reasons were given by participants for preferring CCE over COL including it being less invasive and embarrassing, easier, less painful, quicker, less stressful, more effective and better for the NHS (reasons cited by between 4 and 40 patients, see Table 20 for details). Some preferred COL over CCE, and amongst the reasons given were

bowel preparation, pain and discomfort, efficiency in ability to find and treat pathology, problems during the procedure and use of the belt (reasons given by ≤16 patients each, see Table 20 for details).

Summary: Overall, even though satisfaction and comfort were often better for CCE, there was some evidence that CTC and COL patients were, in the same medical circumstances, more likely than CCE patients to undergo themselves or recommend to a friend the procedure they had undergone. Since satisfaction and comfort were generally greater for CCE and CTC than COL, this perhaps indicates that the medical circumstances impact on a patient's willingness to undergo/recommend an unpleasant test. Reasons for preferring CCE over COL related to patient comfort and convenience. Fewer patients were willing to undergo CCE if they were told that a follow-up COL would be necessary, and some preferred COL due to its ability to find and treat pathology.

Other aspects of patient preference: Some patients in the Wales Pilot Study[34] noted that they had anxiety before the test, but this passed after it. Bond *et al*.[66] (ScotCap) noted additional problems with the belt/holster including patients not understanding the signalling mechanism, and that they could not be easily hidden.

Conclusions drawn by each study's authors: Ismail *et al*.[45] concluded that CCE has a higher satisfaction and comfort rating than COL, and that it should be considered as an alternative to COL in selected individuals. Ojidu *et al.*[71] concluded that patient tolerance and experience favoured CTC and CCE over COL. Bond *et al*.[66] (ScotCap) noted that patients perceived significant value in CCE, but highlighted the importance of clear and accessible information and managing patient expectations. In the discussion section they noted that some refinements to the belt and recorder had already been made in response to the feedback received.

Table 20: Patient/public preference and satisfaction data

Author, year Patient group	Satisfaction	Dissatisfaction	Comfort/ discomfort	Overall preference	Other outcomes
Symptomatic patients					
Ojidu 2018[71] Symptomatic patients	Patient experience 0–10 VAS (direction NR, assume lower better)*; including both bowel preparation and the procedure **COL:** 5.43 **CTC:** 2.35 **CCE:** 3.80 *p*<0.001 COL compared to CTC or CCE: *p*<0.0001 CTC compared to CCE: *p*<0.002	NR	GCS (higher worse pain) **COL** Mean GCS +/- SE: 3.32 ± 0.085 **CTC** Mean GCS +/- SE: 1.96 ± 0.083 **CCE** Mean GCS +/- SE: 1.30 ± 0.088 *p*<0.0001 Nausea from bowel prep **COL:** 16% **CTC:** 5% **CCE:** 39% Bloating from bowel prep: **COL:** 17% **CTC:** 1% **CCE:** 20% Pain from bowel prep: **COL:** 6% **CTC:** 2% **CCE:** 13% *p*<0.0001 for all comparisons	Willing to have procedure again under same medical circumstances: **COL:** 94% **CTC:** 96% **CCE:** 86% CTC compared to CCE *p*=0.01 COL compared to CCE or CTC not statistically significant Undergo same test for screening in 5 years: **COL:** 66% **CTC:** 66% **CCE:** 69% Advise friend to undergo same test under same medical circumstances: **COL:** 96% **CTC:** 100% **CCE:** 88% COL vs. CTC: *p* = 0.535; COL vs. CCE: *p* = 0.001; CTC vs. CCE: *p* = 0.002	None

Author, year Patient group	Satisfaction	Dissatisfaction	Comfort/ discomfort	Overall preference	Other outcomes
Ismail 2022[45]	10-point Likert scale (1 negative, 10 positive) **Mean (range)** CCE: 8.3 (3-10) COL 7.7 (1–10) *p*= 0.2	**Main cause** CCE: bowel preparation and booster medication n=10/40 (25%) COL: pain and discomfort n= 13/40 (33%)	Comfort on a 10-point Likert scale (1 negative, 10 positive) **Mean (range)** CCE: 9.2 (6–10) COL: 6.7 (1–10) *p* <0.0001	Choice of test for future investigation: 77.5% (n = 31/40) preferred CCE Of these, 77.4% (n=24/31) still preferred CCE if a follow-up COL was required after CCE	None
Wales pilot study[34]	All patients reported experience was good or very good Patients liked being able to leave the hospital whilst CCE passed through Patients trusted the procedure before and even more after having it Patients felt treated with respect	Some felt improvements to patient information needed	Some felt belt and recorder were uncomfortable to wear	NR	Most were happy to let AI read the images to be reviewed by a specialist Some had anxiety and concern before the test, which passed after the test
Lay public					
Ojidu 2018[71] Lay public				If symptomatic, which test would they prefer?: **COL:** 45% **CTC:** 37% **CCE:** 18% *p*=NR	

Author, year Patient group	Satisfaction	Dissatisfaction	Comfort/ discomfort	Overall preference	Other outcomes
Symptomatic and surveillance patients					
Bond 2023[66]	**CCE capsule:** easier to swallow than expected (n=19) **Information and communication:** 111/151 satisfied, mentioned helpful staff (n=14), friendly (n=74) pleasant (n=11), reassuring (n=7), telephone calls highly informative (n=42) **Impact on daily life:** n=72 stated positive impact, including less travel, complete at home, flexibility to do other things, saved time, normal routine continued	**Bowel preparation:** amount of liquid and longer process than endoscopy (n=28); bad taste (n=13) *Also mentioned:* longer process than COL, toileting accidents, needing help from relatives for daily tasks **CCE capsule:** dissatisfaction after swallowing (n=17) (see column 4 for reasons) **Results:** n=3 dissatisfied because had to wait for result and then wait for COL, results not clear due to bowel preparation **Information and communication:** 46 dissatisfied, mentioned information inadequate (n=27) or not clear (n=26), uninformed after swallowing the capsule (n=9) and about process involved	**Bowel preparation:** pain discomfort (n=8) *Also mentioned:* feeling unwell, feeling bloated, longer bowel motions, bleeding **CCE capsule:** pain and discomfort after swallowing (n=10), prolonged fasting (n=9), insecurity as no staff around (n=3) **Belt/holster:** heavy and bulky (n=15), uncomfortable and cumbersome (n=14), requiring constant adjustment (n=6), restricting activities (n=6)	**Comparing CCE to COL:** *Preferred CCE because:* less invasive/ embarrassing (n=40), easier (n=20), less painful (n=26), quicker (n=13), less stressful (n=8), more effective (n=7), better for the NHS (n=4). *Preferred COL because:* bowel preparation (n=7), pain and discomfort (n=5), time needed and ability to find and treat a pathology) (n=16), possibility of still needing further investigations if undergoing CCE (n=8), and others (pain and discomfort, fasting, problems during the procedure, information given, and use of a belt).	**Belt/holster:** did not understand signalling mechanism (n=7) *Also mentioned:* could not be easily hidden

Author, year Patient group	Satisfaction	Dissatisfaction	Comfort/ discomfort	Overall preference	Other outcomes
		after the procedure (n=5), information provided overwhelming (n=4). misunderstanding about level of involvement needed for procedure (n=15), confusion with the entire process (n=11), including preparation (n=5), lack of information about the risks of CCE and its advantages and disadvantages (n=3) **Impact on daily life:** negative impact (n=10). *Also mentioned:* activities limited/negatively impacted by laxative and wearing recorder belt, such as needing a bathroom nearby, not working/showering, impact on travel with bowel preparation and distance		Majority of patients would recommend CCE (n=162), 6 patients would not recommend, 29 patients were not sure.	

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; VAS - visual analogue scale; GCS - Gloucester Comfort Scale; AI - artificial intelligence; SE - standard error; NR - not reported

** Based on text which states "OC* [optical colonoscopy] *scored less well than both CTC (p<0.0001) and CCE (p<0.0001)."*

3.3.5 Ongoing studies

A number of ongoing studies were identified by the systematic review (see Table 21). Six studies[89-94] were identified through searches of trial registries, and one study[95] was found through chance finds (an *ad hoc* google search).

A UK diagnostic test accuracy study called ColoCap[95] is ongoing until 2027. This appears to be a true diagnostic test accuracy study, and will recruit suspected CRC, suspected IBD and post-polypectomy surveillance patients. It was not clear if the CCE used would be PillCam COLON 2, but the study aims to report sensitivity and specificity, patient acceptability and various other outcomes of relevance. The outputs from this study are likely to be highly relevant to the current decision problem, if the device used is PillCam COLON 2. It will likely have better external and internal validity than the current evidence presented in this report, and depending on sample size and study methodology details, may represent a preferable source of both diagnostic test accuracy and prevalence estimates.

One Danish study[93] is an RCT of CCE compared to COL. This study plans to report clinical outcomes as well as diagnostic test accuracy, though it was unclear from the information available whether the latter would be sensitivity and specificity of CCE with a reference standard of COL in all patients. It was also unclear whether symptomatic patients in Denmark will be similar to those in the UK in terms of referral criteria, and whether PillCam COLON 2 will be used.

Another Danish study[91] from the same hospital used PillCam COLON 2 and recruited patients with incomplete COL, a referral for COL under general anaesthesia or declining COL after completion of bowel preparation. It was unclear if all patients would receive a reference standard of COL.

Another UK study[92] aimed to look at the delivery of CCE using fifth generation (5G) wireless technology. This study may have completed in 2023 based on the trial registry record, but no publication reporting findings was identified by the EAG. This was not a test accuracy study, but would report patient acceptability and feasibility.

Three other studies, one from the Netherlands[94, 96] and two from Japan, [89, 90] should have completed >5 years ago based on the trial registry record, but no publication reporting findings was identified by the EAG.

One further study,[97-99] reported as an interim analysis, is worthy of note. The capsule endoscopy delivery at scale through enhanced AI analysis (CESCAIL) study did not meet our inclusion criteria as there was apparently no independent reference standard planned. However, the development of the technology in this direction is interesting to note.

Table 21: Relevant ongoing studies and studies that have not yet reported

Title Country Study design	Start and end dates	Population	Intervention Comparator/reference standard	Outcomes of relevance
Studies that have not completed yet				
ColoCap: Determining the diagnostic accuracy of colon capsule endoscopy compared to standard colonoscopy in patients at risk of colorectal disease.[95] UK Diagnostic test accuracy	2024-2027	Suspected CRC, suspected IBD and post-polypectomy surveillance	Intervention: CCE (does not state whether PillCam Colon 2) Comparator/reference standard: COL	Sensitivity and specificity Patient acceptability Various other outcomes of relevance
Camera Capsule Endoscopy in the Routine Diagnostic Pathway for Colorectal Diseases[93] Denmark RCT	2024 - 2025	Symptomatic patient referred for COL, aged >18 years	Intervention: NR, possibly PillCam based on other study[91] in Odense University, Denmark Comparator/reference standard: COL	Sensitivity and specificity Cost of CCE vs. COL pathways Various other outcomes of relevance
Safety Of ColoRectal Assessment and Tumor Evaluation by Colon Capsule Endoscopy[91] Denmark Observational	2020 - 2030	Incomplete COL, referral for COL under general anaesthesia or declining COL after completion of bowel preparation.	Interventions: PillCam Colon 2 Comparator/reference standard: Unclear, at least some will receive COL	Sensitivity and specificity (depending on reference standard) Patient preference
Studies that may have completed but no published results found by EAG				
Trial Feasibility of Home Delivery of Colon Capsule Endoscopy Service With the Help of 5 G Technology[92] England Observational	2022-2023	Patients who have been selected by overseeing clinician meeting NHS England criteria to undergo CCE as part of their standard of care. Age between 18-55 years.	Intervention: CCE at home, using 5G technology, type NR	Feasibility and patient acceptance

Evaluation of PillCam Colon 2 in Visualisation of the colon[94] Netherlands Diagnostic test accuracy	NR, study registered in 2010	Patients referred to COL for at least one of the following reasons: - CRC screening for age >50 - Clinical symptoms such as: rectal bleeding, haematochezia, melena, positive FOBT, recent change of bowel habits for age >50 - Positive findings in the left colon during sigmoidoscopy(e.g. polyp >10mm) - Personal history of polyps that were removed at least 3 years ago	Intervention: PillCam Colon 2 Comparator/reference standard: COL	Sensitivity and specificity
Open-label randomised comparative study of the detection rates of colorectal tumours/polyps between colon capsule endoscopy and CT colonography[89] Japan RCT	NR, study registered 2014	Patients with positive FIT or symptoms suspicious of harbouring colorectal tumours or polyps	Intervention: unclear which colon capsule Comparator/reference standard: COL	Sensitivity and specificity
A clinical study comparison between two groups of intestinal tract cleansing agents for CCE based on the COL as a golden standard, and usefulness of interpretation support by clinical engineering technologist[90] Japan RCT of bowel cleansing, but all patients get CCE and COL	2017-2018	Symptomatic patients referred for COL	Intervention 1 & 2: different bowel cleansing methods All patient receive both CCE and COL. Unclear which CCE technology	Sensitivity and specificity Other outcomes including bowel cleansing rates

CRC - colorectal cancer; IBD - inflammatory bowel disease; COL - colonoscopy; CTC - computed tomography colonography; RCT - randomised controlled trial; NR - not reported; 5G - fifth generation

3.4 Discussion

Summary of the evidence

Because there were insufficient data fully meeting the initial inclusion criteria for the review, the criteria were widened where necessary. This led to the inclusion of three evidence types: (i) diagnostic test accuracy studies to provide evidence on the sensitivity and specificity of CCE; (ii) diagnostic yield studies to provide estimates of prevalence and capacity spared, and (iii) patient preference studies. In total, the review included: one diagnostic test accuracy study[57] that met the original inclusion criteria for the review, conducted in a symptomatic population; five diagnostic test accuracy studies that met widened criteria for the review, conducted in mixed populations;[42, 46, 60, 75, 77] four diagnostic yield studies (reported across seven publications)[31-34, 40, 68, 78] that met widened criteria for the review, and were conducted in symptomatic or surveillance populations; seven diagnostic yield studies[53, 56, 58, 62, 72, 73, 76] that met widened criteria for the review, and were conducted in patients with incomplete COL or patients who had refused COL; and four studies (reported across 5 publications)[34, 45, 63, 66, 71] that met the original inclusion criteria for the review (or for surveillance populations, widened criteria) and were on patient preference.

A summary of the data is provided in Table 22. A summary of the data of most relevance to the decision problem follows. Sensitivity and specificity for clinically significant polyps was calculated by the EAG to be 100% (95% CI calculated by EAG:[81] 0.65-1.00) and 98% (95% CI calculated by EAG:[81] 0.91-1.00), respectively, in one small study[57] (n=66 patients, 7 significant polyps) conducted in symptomatic patients referred according to NICE criteria at the time of the study (prior to 2021). In studies with mixed populations that included at least some of the patients defined in the final NICE scope[35] (i.e., symptomatic or post-polypectomy surveillance patients), the EAG's pooled analysis estimated sensitivity and specificity for polyps of any size (n=2 studies)[46, 60] to be 0.75 (95% CrI: 0.51, 0.90) and 0.60 (95% CrI: 0.27, 0.88), respectively; for polyps ≥6mm (n=4 studies)[42, 46, 75, 77] sensitivity and specificity were 0.83 (95% CrI: 0.70, 0.91) and 0.69 (95% CrI: 0.52, 0.81), respectively; and for ≥10mm (n=4 studies)[42, 46, 75, 77] sensitivity and specificity were 0.85 (95% CrI: 0.70, 0.94) and 0.90 (95% CrI: 0.82, 0.95), respectively. Data on the diagnostic test accuracy for adenomas were limited to one small study (n=89 patients) with potentially poor generalisability to the decision problem.[46] Four studies[31-34, 40, 68, 78] reported diagnostic yield in the scope-defined populations. These studies reported the numbers of polyps identified for various size categories, but the data of perhaps most interest relate to subsequent tests and discharge rates, where COL was spared in 50%[33] to 37%[31] (n=3 studies)[31, 33, 40] of symptomatic patients, but in fewer surveillance patients at 27%[31] (various surveillance patient types) and [redacted] (3-year post-polypectomy patients). Seven studies[53, 56, 58, 62, 72, 73, 76] were included in patients who refused or had an incomplete COL in mixed populations. The proportion within the scope of the assessment ranged from 52%[58] to 74%.[76] The number of COL referrals post-CCE ranged from 26%[62] to 70%[53] across the studies.

Table 22: Summary of the findings of the review

Subgroup of studies	Number of studies included Total N	Bowel cleansing range Completion rates range	AEs, technical failures (n=number of studies reporting the outcome)	Key findings Sensitivity (95% CI or CrI)* Specificity (95% CI or CrI)* (n=number of studies reporting the outcome)	EAG's view on strengths	EAG's view on limitations
3.3.2.1: DTA meeting inclusion criteria	1 study[57] 66	• 92% • 76%	NR	**Clinically significant polyps** • Sens 100% (95% CI:81 0.65-1.00) • Spec 98% (95% CI:81 0.91-1.00)	Relevant population: Symptomatic patients referred using NICE criteria	Small single centre study; EAG calculated data; does not report data by size of polyp; no data for post-polypectomy surveillance
3.3.2.2: DTA in mixed populations	5 studies[42, 46, 60, 75, 77] 4 statistically synthesised 369	• 61%[42] to 91%.[46] • 74%[60] and 89%[46] (n=2 studies)	• AEs: ≤5%, related to bowel prep (n=3 studies) [60, 75, 77]; no serious AEs (n=1 study);[42] fatigue (n=1 study) [77] • Tech failure: 1%[75] and 3%[77] (n=2 studies)	**Any size polyps (n=2): [46, 60]** • Sens 0.78 (0.51-0.90) • Spec 0.60 (0.27-0.88) **Polyps ≥6mm (n=4) [42, 46, 75, 77]** • Sens 0.83 (0.70-0.91) • Spec 0.69 (0.52-0.81) **Polyps ≥10mm (n=4) [42, 46, 75, 77]** • Sens 0.85 (0.70-0.94) • Spec 0.90 (0.82-0.95) **Polyps 6-9mm (n=1) [46]** • Sens 0.63 (0.50-0.74) • Spec 0.76 (0.68-0.83)	Studies are true diagnostic test accuracy studies	Studies are in the wrong populations Multiple sources of clinical and methodological heterogeneity High levels of statistical heterogeneity in the syntheses

Subgroup of studies	Number of studies included Total N	Bowel cleansing range Completion rates range	AEs, technical failures (n=number of studies reporting the outcome)	Key findings Sensitivity (95% CI or CrI)* Specificity (95% CI or CrI)* (n=number of studies reporting the outcome)	EAG's view on strengths	EAG's view on limitations
				Adenomas Sensitivity and specificity data limited to 1 study[46] (see Table 11)		
3.3.3.1: Yield: correct population	4 studies[31-34, 40, 68, 78] 5,678 (Note: 1 study did not report n analysed)	• 62%[33] to 86%[34] • 69%[34] to 72%.[31] (n=3 studies) [31, 34, 40]	• **AEs**: ScotCap:[31] inability to swallow (1.6%), dehydration (0.2%), problems with bowel preparation (1.3%), Mallory-Weiss tear from vomiting (0.2%); [redacted] • **Retentions:** were 0.2%[31] and [redacted][40] (n=2 studies) • **Tech failure:** 0.3% (n=1 study) [31]	No statistical synthesis **Capacity spared** • Symptomatic: 50%[33] - 37%[31] (n=3 studies)[31, 33, 40] • Surveillance: 27%[31] and [redacted] (n=2 studies) Numbers with polyps also reported	Studies were in the correct populations for some studies, therefore estimates of capacity spared and polyp prevalence likely to have good generalisability	Studies did not give all participants a reference standard and therefore have not ascertained the number of diagnoses missed by CCE Unclear what criteria would be used to refer patients to CCE in clinical practice, may affect generalisability of data
3.3.3.2: Yield: incomplete or refused COL	7 studies[53, 56, 58, 62, 72, 73, 76] 1,137	• 54%[53] to 92%[76] • 40%[53] to 77%[72]	• AEs: 3 studies[53, 58, 72] reported no AEs, 1 did not report AEs,[56] 4 studies[62, 72, 73, 76] reported AEs including nausea, vomiting, headache,	**COL referrals:** • 26%[62] to 70%.[53] Number with polyps detected by CCE also reported	Provides data on patients who refused or had incomplete COL	Studies did not give all participants a reference standard and

Subgroup of studies	Number of studies included Total N	Bowel cleansing range Completion rates range	AEs, technical failures (n=number of studies reporting the outcome)	Key findings Sensitivity (95% CI or CrI)* Specificity (95% CI or CrI)* (n=number of studies reporting the outcome)	EAG's view on strengths	EAG's view on limitations
	(range 50[76] to 689)[56]	• Completed COL: 70%[58] to 98%[62]	vertigo, abdominal pain, retentions • Retentions: 1%;[62] 2%;[76] 3%;[72] 1%[73] • Tech failure: 1%[73] (n=1 study)	Relative sensitivity between CCE and CTC reported but with limitations (n=2)[58, 62]		therefore have not ascertained the number of diagnoses missed by CCE. Number of referrals is dependent on the pre-test probability of a positive result (i.e., the prevalence of disease in the sample), study samples not generalisable
3.3.4: Patient preference	4 studies[34, 45, 63, 66, 71] >693 (1 study did not report numbers) [34]	N/A	N/A	• Patients generally satisfied with CTC>CCE>COL, citing comfort and convenience • Some discomfort, e.g., wearing belt, bowel preparation, swallowing pill • More CTC vs CCE (p=0.01) and more COL vs CCE (p=not significant) patients preferred	3 studies[34, 66, 71] conducted as part of routine practice, therefore good generalisability	Little data on surveillance population Some methodological flaws

Subgroup of studies	Number of studies included Total N	Bowel cleansing range Completion rates range	AEs, technical failures (n=number of studies reporting the outcome)	Key findings Sensitivity (95% CI or CrI)* Specificity (95% CI or CrI)* (n=number of studies reporting the outcome)	EAG's view on strengths	EAG's view on limitations
				test in same medical circumstances • Informed public preferred COL>CTC>CCE if symptomatic (*p*=NR)		

AE - adverse event; CI - confidence interval; CrI - credible interval; DTA - diagnostic test accuracy; EAG - External Assessment Group; NICE - National Institute for Health and Care Excellence; DTA - diagnostic test accuracy; CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; NR - not reported; N – number; Tech - technical
** Sensitivity and specificity based on data reported in the discussion; 95% CI calculated by EAG.*[81]

Across all studies, bowel cleansing rates ranged from 54%[53] to 92%.[57] Bowel cleansing regimens were fairly variable, though most used PEG and bisacodyl. It was not an objective of this assessment to investigate which bowel cleansing regimen is optimal, but the regimen may affect cleansing levels achievable in clinical practice. Completion rates were generally defined as complete visualisation of the colon within the battery life of the capsule, and ranged from 40%[53] to 89%[46] and were most variable in studies of patients with incomplete COL or who refused COL, though this category also contained the largest number of studies (n=7). Five of these seven studies also reported completion rates including CCEs that completed an incomplete COL. According to this metric, complete visualisation of the colon was achieved in a higher proportion of patients, from 70%[58] to 98%.[62] AEs were largely related to bowel preparation and were relatively uncommon (usually <5%), though not all studies reported AEs, and the AEs that were reported may be only those severe enough to warrant reporting. Patient preference studies indicated that the bowel preparation regimen was a source of pain, discomfort and dissatisfaction amongst participants. Technical failures and retentions were not reported by all studies which may indicate they did not occur, and where they were reported, they were relatively rare (≤3%).

Across the four studies of patient preference, patients varied in their opinions. There was general satisfaction with CCE (e.g., convenience, communication and friendly staff), and some evidence that patients were most satisfied with CTC, but more were satisfied with CCE compared to COL. Dissatisfaction centred around the bowel preparation, pain after swallowing the pill, the wait for CCE results and a subsequent COL where necessary, the impact on daily life (bowel preparation and wearing the belt/recorder), and aspects of patient information. However, with respect to preference, there was some apparently conflicting information, with one study[45] noting more patients who had a COL or CTC would recommend the test to a friend than those who had a CCE (96% vs 94% vs 88% respectively, p=0.001), but in another study[66] there were more instances of reasons to prefer CCE than COL (although it was not clear if the total number who preferred CCE was greater). One study[45] noted that the number who would choose CCE for a future investigation (n=31/40) fell to 24/40 if they were told a follow-up COL would be required. Informed members of the public chose CCE as their test of preference the least often (18%), with COL being the most popular (45%) followed by CTC (37%). There were limited data for post-polypectomy surveillance patients, and it is unclear if the findings are generalisable to this population.

The following sections provide a more detailed discussion of each evidence type in turn, considering the decision problem and the NICE scope,[35] and any strengths and limitations identified by the EAG.

Discussion of diagnostic test accuracy data (Section 3.3.2)

The one study[57] that was identified that met the initial inclusion criteria for the review recruited symptomatic patients only and was a small single-centre study that did not report data per polyp size. This study reported data for "significant polyps", though the definition was uncertain, and the sensitivity and specificity data were calculated by the EAG based on information provided in the discussion. Due to the small sample size (n=66), the small number of patients with significant polyps (n=7), and the lack of data for patients post-polypectomy, these data were considered insufficient for use in the EAG's economic model, and further data were sought.

Upon widening the inclusion criteria relating to the population to include studies of mixed populations, five studies[42, 46, 60, 75, 77] were included. The proportion of patients likely to be within the scope of the assessment varied from 64%[77] to potentially as little as 11%.[46] The EAG is uncertain how generalisable these studies in mixed populations will be to the patients in whom CCE would be used in practice in England. It could be argued that a polyp is a polyp, and the accuracy of the test is likely to be similar regardless of the population. However, it could also be argued that the distribution of stages and sizes for polyps and CRCs are likely to differ between populations, especially where patients are symptomatic compared to where they are not (e.g., screening populations), and where a patient has already had a polypectomy 3 years previously compared to patients who have not had any colonic investigations before, or patients who have not had polyps before. It is not possible to predict what impact these potentially competing factors may have on test accuracy. But if test accuracy is different according to the size of the polyp, and the distribution of polyp sizes differ by population, the overall test accuracy could reasonably be expected to be different. The EAG notes that the lack of studies in the correct population is a limitation of this assessment and introduces uncertainty.

A statistical synthesis to pool the data from four of these studies that had compatible outcomes (see Table 23) indicated that both sensitivity and specificity improved numerically as polyp size increased. Statistical tests were not undertaken to assess whether test accuracies were statistically significantly different to one another according to polyp size, and sample sizes may be too small to detect meaningful differences regardless.

There are several existing systematic reviews on CCE, which have used various inclusion and exclusion criteria, and which report various estimates of sensitivity and specificity. Some of the most recent reviews, alongside Spada *et al.* 2016,[100] are reported in Table 23. None of the reviews included all of the same studies as each other, and most excluded both Morgan 2016[42] (possibly due to the unusual terminology used to describe CCE in this paper, meaning it was difficult to pick up in systematic searches, see Section 3.1.2) and Omori 2024,[46] which was published more recently than the reviews. The estimates of sensitivity for polyps ≥6mm ranged from 0.83 (the EAG analysis) to 0.88 (Mollers 2021),[101] whilst specificity ranged from 0.69 (the EAG analysis) to 0.88 (Spada 2016[100] and Ali 2021).[102] For polyps ≥10mm, sensitivity ranged from 0.85 (the EAG analysis) to 0.89 (Mollers 2021),[101]

whilst specificity ranged from 0.90 (the EAG analysis) to 0.96 (Ali 2021).[102] The EAG's analysis produced the lowest estimates of diagnostic test accuracy in all cases, possibly due to the different inclusion criteria (we excluded exclusively screening populations), and the inclusion of Omori 2024,[46] which had low estimates of sensitivity and specificity compared to the earlier studies. In one of the sensitivity analyses conducted by the EAG, Omori 2024[46] was excluded and estimates of sensitivity and specificity increased, but were not as high as in the existing reviews (see Table 23). The economic model uses data from the EAG's meta-analysis in the base case, but also includes a sensitivity analysis using data from the Spada *et al.* 2016[100] meta-analysis to test how different sensitivity and specificity inputs may affect the cost-effectiveness of CCE (see Section 4.3). Scenarios were also conducted assuming CCE has the same test accuracy as COL and CTC.

Diagnostic accuracy data on adenomas were only reported by one small study (n=89),[46] but suggested that there is the potential for CCE to miss adenomas of any size. The sensitivity for adenomas <6mm was particularly poor at 0.59 (95% CI 0.49-0.67), with poor specificity at 0.65 (95% CI 0.50-0.78).[46] As with polyps, the best test accuracy was reported for adenomas ≥10mm, where sensitivity was 0.81 (95% CI 0.65-0.91) and specificity was 0.91 (95% CI 0.86-0.94).[46] Two studies[75, 77] reported that CCE detected 100% of CRC cases. However, data were limited with extremely low numbers of events (n=1[75] and n=3).[77]

The relevance and interpretation of the available evidence depends in part on what findings on CCE would trigger a referral for COL. Were polyps ≥6mm seen on CCE used to indicate referral for COL, CCE would likely miss as few as 9% of patients with polyps of that size, or as many as 30%, with a point estimate of 17%. It would also result in as many as 48% or as few as 19% of patients without polyps ≥6mm being sent for COL who did not need one, with a point estimate of 31%. However, it would reduce the number of referrals to COL, and this is explored in more detail in Chapter 4. If all patients with polyps ≥10mm seen on CCE were referred for COL, the proportions missed appear similar to polyps ≥6mm, but proportionately fewer would be sent for COL who do not need one (see Table 23). However, this strategy would mean that patients with only polyps <10mm seen on CCE are not treated, and it is possible that some of these may be adenomatous or cancerous, or may become so over time. Similarly, using polyps of size ≥6mm to determine referral would mean patients with only polyps <6mm are not treated. Data for "polyps of any size" were limited, with only two studies reporting this, but pooling indicated that CCE could miss as many as 49% of such polyps, or as few as 10%, with a point estimate of 22%.

A further referral option is to use the ESGE criteria of ≥3 polyps or one or more polyps ≥6mm.[27] Only one study[57] reported data for this category (though there was some uncertainty as to the precise definition, which was reported as >3 polyps or one or more polyps >6mm), where sensitivity was 100% (95% CI calculated by EAG:[81] 0.65-1.00) and 98% (95% CI calculated by EAG:[81] 0.91-1.00). However,

these data come from the one small (n=66) study that met the initial inclusion criteria, and which had a small number of events (n=7). It is not possible to conclude if this indicates that test accuracy is superior in this category of disease compared to per-patient test accuracy for various sizes of polyps as determined in the studies with mixed populations.

Sensitivity analyses relating to the pooled analyses indicated that removing Omori *et al.*[46] due to its somewhat different recruitment criteria increased the pooled estimates. However, this was the only non-industry funded study and the most recent study, and it is difficult to draw conclusions as to why this study reported lower sensitivity and specificity, or which analysis has the highest applicability. As anticipated, a sensitivity analysis using a non-informative prior made very little difference to point estimates but widened the CrIs. The EAG prefers to use a weakly informative prior distribution for the between-study variation in the base case as there are only four studies included in the analysis.

Table 23: Summary of meta-analyses of sensitivity and specificity by polyp size from the EAG's analysis and from recent systematic reviews

Polyp size	Number of studies	Pooled sensitivity (95% CrI or CI)	Pooled specificity (95% CrI or CI)
EAG's analysis (studies including at least some symptomatic or polyp surveillance patients)			
Any size (95% CrI)	2	0.78 (0.51-0.90)	0.60 (0.27-0.88)
≥6mm (95% CrI)	4	0.83 (0.70-0.91)	0.69 (0.52-0.81)
≥10mm (95% CrI)	4	0.85 (0.70-0.94)	0.90 (0.82-0.95)
EAG's sensitivity analysis removing Omori 2024[46]			
Any size	N/A	N/A	N/A
≥6mm (95% CrI)	3	0.86 (0.69-0.95)	0.72 (0.54-0.85)
≥10mm (95% CrI)	3	0.88 (0.68-0.97)	0.91 (0.78-0.96)
Kjolhede 2021[103] (any population)			
Any size	4	0.85 (0.73-0.92)	0.85 (0.70-0.93)
≥6mm	6	0.87 (0.83-0.90)	0.88 (0.75-0.95)
≥10mm	5	0.87 (0.82-0.90)	0.95 (0.92-0.97)
Ali 2021[102] (any population, multi-centre studies only)			
Any size	NR	NR	NR
≥6mm	5	0.86 (0.82-0.91)	0.88 (0.72-0.96)
≥10mm	5	0.86 (0.8-0.91)	0.96 (0.92-0.98)
Mollers 2021[101] (various populations)			
Any size			
≥6mm (FIT+ screening, first degree relatives and mixed populations)	5	0.88 (0.82-0.93)	0.80 (0.69-0.87)
≥10mm (first degree relatives and mixed populations)	4	0.89 (0.79-0.94)	0.93 (0.89-0.95)
Spada 2016[100] (any population)			
Any size	NR	NR	NR
≥6mm	6	0.86 (0.82-0.89)	0.88 (0.74-0.95)
≥10mm	7	0.87 (0.81-0.91)	0.95 (0.91-0.97)

EAG - External Assessment Group; CrI - credible interval; CI - confidence interval; FIT - faecal immunochemical test; NR - not reported

Assessment using the QUADAS 2 tool indicated low risk of bias for most items, but some limitations of the studies, including concerns about the applicability (generalisability) of the patient populations.

Studies exist that tested different bowel preparation regimens, but a review of these was beyond the scope of this assessment.

There were further limitations to the diagnostic test accuracy data. The variability in inclusion criteria introduced some between-study clinical heterogeneity to the analysis, and statistically, the between-study heterogeneity was moderate to high. There were other sources of heterogeneity amongst the studies, including variations in bowel preparation regimens, polyp matching criteria and whether incomplete CCEs were included in the analysis of test accuracy. Due to the small number of studies and multiple sources of heterogeneity, it was not possible to investigate the effects of these sources of heterogeneity, and they introduce some uncertainty regarding the generalisability of the results to the use of the test in clinical practice.

Discussion of diagnostic yield studies

Studies in symptomatic and surveillance populations defined in the scope

Four studies[31-34, 40, 68, 78] were included after widening the inclusion criteria to include studies of diagnostic yield in symptomatic and surveillance populations. Diagnostic yield studies do not routinely test patients who did not have a positive CCE test and therefore FNs and TNs cannot be ascertained. These studies therefore do not report sensitivity and specificity and do not assess diagnostic test accuracy. Whilst all four studies reported data relating to the number of polyps identified in various size categories by CCE, this does not provide information about the number of missed diagnoses.

The most clinically interesting data from yield studies are perhaps those relating to capacity spared, i.e., how many COLs would be avoided through use of CCE. Estimates ranged from 50%[33] to 37%[31] (n=3 studies)[31, 33, 40] in symptomatic patients, and were, perhaps unsurprisingly, much lower in surveillance populations, at 27%[31] (various surveillance patient types) and [redacted] (3-year post-polypectomy patients).

The pre-test probability of a positive CCE (i.e., how many patients in the sample have relevant bowel pathology), which will be determined by the patient population recruited, will affect capacity spared estimates as well as estimates of diagnostic yield, and should be taken into consideration when interpreting the evidence base. With respect to the population recruited, all four studies were conducted in the UK. The study of highest relevance to the decision problem is likely to be the NHSE CCE Pilot Study which was conducted in 55 centres in England.[32] However, as it is unclear what criteria would be used to select patients for CCE should it be recommended for use in England, the generalisability of the NHSE CCE Pilot Study data to this future population are somewhat uncertain. The referral criteria in

Scotland differ from England, and the ScotCap study is therefore less relevant than the NHSE CCE Pilot Study. The two remaining studies are also of relevance as they recruited symptomatic patients with FIT <10µg/g[34] and FIT 10-100µg/g,[33] but the Wales study did not report capacity spared. Therefore the estimates of capacity spared of highest relevance are as follows: FIT <10µg/g: [redacted],[40] FIT10-100µg/g:[33, 40] [redacted] and 50% and post-polypectomy surveillance: [redacted].[40] It is unclear how many diagnoses were missed amongst these patients who did not receive a subsequent test (e.g., COL or FSIG).

The data on test uptake from the diagnostic yield studies are also useful, as this outcome was difficult to assess in experimental studies such as the diagnostic test accuracy studies where non-uptake of the test may be due to factors associated with the experimental nature of the study (e.g., having to undergo both a CCE and a COL). For this outcome, the routine practice nature of these studies is an advantage. ScotCap[31] was the only study to provide data on test uptake. In this study, reasons for not accepting the referral were related to CCE 73 times. However, since more than one reason could be counted per patient, it was unclear how many patients this related to.

Studies in patients with incomplete COL or who refused COL

Seven studies[53, 56, 58, 62, 72, 73, 76] were included after widening the inclusion criteria to include studies of patients with incomplete or who refused COL, where >50% were referred to COL for reasons listed in the NICE scope.[35] None of the studies had populations that matched the NICE scope, and it is therefore difficult to draw conclusions as to the likely impact of this test on the need for subsequent COL as the pre-test probability will affect post-CCE referral rates. Within these studies, the number of COL referrals post-CCE ranged from 26%[62] to 70%,[53] where reported.

It was, however, interesting to note that using CCEs in patients with incomplete COLs could complete an incomplete examination of the colon; when completion rates were calculated including CCEs that completed incomplete COLs, the range of rates changed from 40%[53] to 77%[72] to 70%[58] to 98%.[62]

The relative sensitivity reported versus CTC was based on TPs and indicated that CCE probably identified more TP polyps than CTC, but the metric did not indicate the number of FPs which may generate unnecessary COLs, or the number of FNs. Data on FPs (i.e., polyps not confirmed after COL) was limited, and ranged from 52%[56] for significant polyps (≥6 mm and/or ≥ 3 polyps) to 4% for polyps ≥6mm.[62] The reasons for the wide variation in estimates is unclear, but may be due to variable patient populations.

Discussion of patient preference studies

Four studies were identified, all of which included symptomatic patients and one of which included some surveillance patients of relevance, but no data were available for surveillance populations

separately. This is a limitation of the evidence base, if patient preference were to differ according to indication.

Three of the studies[34, 66, 71] were conducted in patients having the test as part of routine practice, meaning the results should have high applicability to clinical practice. Only one study included patients under surveillance and it was unclear how many of these patients met the definition of polyp surveillance patients listed in the NICE scope.[35] The evidence base is therefore heavily weighted towards patients with symptoms. Only one study had any links to the device manufacturer, indicating that the evidence base is at low risk of bias overall from industry funding. The overall risk of bias as assessed using the MMAT tool was fairly low, but the EAG note some additional limitations. For example, ScotCap used an opportunistic sample rather than purposive sampling, and recruited a smaller number of patients than originally planned. Ismail *et al*.[45] did not give members of the public any indication of how likely a COL would be following a CCE, which may affect patients' perceptions of acceptability, and it was unclear from other studies how well this particular aspect of the test may alter patient preference. Ojidu *et al*.[71] recruited patients who had been assigned to have either a COL, CTC or CCE based on clinical judgement, and it is therefore unclear whether the groups are comparable to each other in terms of risk of pathology or other patient factors that may affect patient preference, putting internal validity (for comparing tests to each other) at risk. However, these data may have high external validity for each test individually if the same criteria would be used to assign patients to different tests in clinical practice. The diagnostic accuracy of each test was not directly addressed in the patient preference studies, with at least one study informing patients that test accuracy was equivalent, which may not be the case.

4. COST-EFFECTIVENESS

This chapter presents a systematic review of published economic evaluations of CCE for detecting colorectal polyps and CRC (Section 4.1), a summary and critique of the economic analysis submitted to NICE by the test manufacturer (Section 4.2) and the methods and results of an independent model-based economic analysis undertaken by the EAG (Section 4.3). A discussion of the key issues around the cost-effectiveness of CCE for detecting colorectal polyps and CRC is presented in Section 4.4. Details of the review and planned economic analyses can be found in the final EAG protocol[39] (available from https://www.nice.org.uk/).

4.1. Review of existing economic evaluations

4.1.1. Review methods

Systematic searches were undertaken to identify existing economic evaluations of CCE in adults with lower GI signs or symptoms suggestive of CRC or in people who are in colonoscopic surveillance. Database searches were undertaken at the same time and using the same population and intervention terms as those used to find diagnostic studies (see Section 3.1.2), but for the purposes of the present review these were combined with the NHS Economic Evaluation Database [NHS EED] filter.

The following databases were searched on the 9th August 2024:

- MEDLINE and MEDLINE in Process and Epub ahead of print (via Ovid)
- EMBASE (via Ovid)
- EconLit (via Ovid)
- HTA Database of the International Network of Agencies for Health Technology Assessment (via the INAHTA website).

In order to keep the number of search results manageable, conference abstracts were excluded from the main EMBASE search. Instead, a targeted search was conducted to find relevant abstracts from the following conference series, selected on the advice of clinical experts, from the 1st January 2014 to the 13th August 2024:

- ASCO
- ESMO
- AACR
- European Cancer Summit
- DDW
- UEGW
- APDW
- BSG Annual Meeting (also known as BSG Live).

Full search strategies are reproduced in Appendix 2. Reference lists of included papers were also checked to minimise the risk of missing any relevant studies. Additional targeted searches were undertaken, where required, to identify additional data for the purpose of populating the EAG's economic model (see Section 4.3).

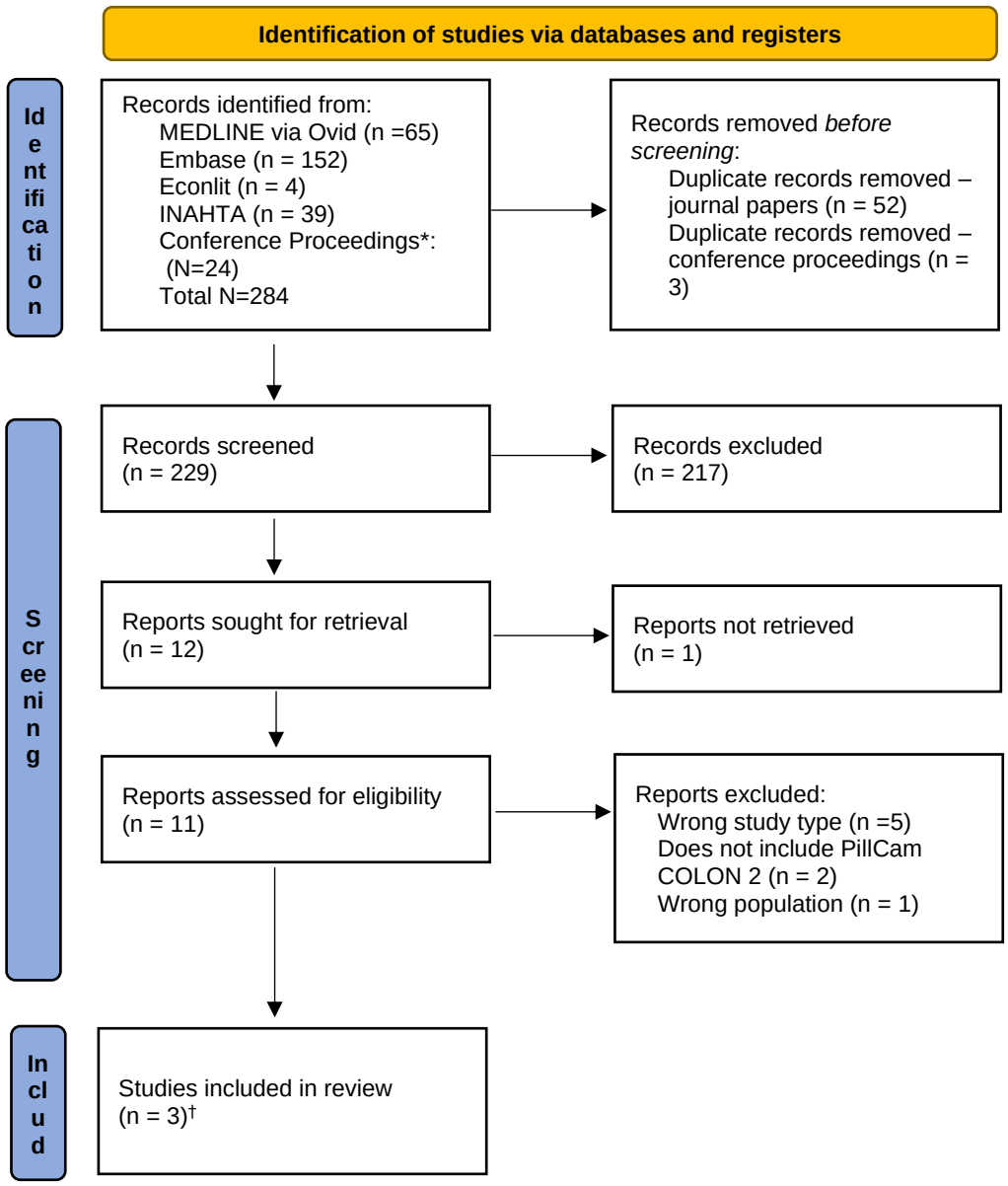
In order to be considered potentially relevant for inclusion in the review, studies were required to meet all of the following criteria:

- Full economic evaluations comparing PillCam COLON 2 versus other diagnostic tests for the detection of colorectal polyps or CRC in people with symptoms of CRC and/or in people who are due to have a post-polypectomy surveillance COL.
- Published in English
- Available in full-text format (studies which were available in abstract form only were excluded from the review)
- Relevant to the intervention and populations included in the final NICE scope.[35] Studies of other types of CCE or the use of CCE for screening in an average-risk population were excluded from the review.

Study selection was conducted in two stages. The first stage involved sifting the titles and abstracts of all studies. The second stage involved reviewing the full-texts of potentially includable studies from the title/abstract sift. Both stages were completed by two reviewers (PT and ANB). Any disagreements about study inclusion at either stage of sifting were resolved through discussion between the reviewers.

A PRISMA diagram which provides details of the studies selected for inclusion in the review is presented in Figure 8. Following de-duplication, the electronic searches identified a total of 229 citations. Of these, 12 studies were deemed to be potentially includable and full-texts were obtained for further scrutiny. One of these studies (Palimaka *et al.*[104]) was a full economic evaluation of CCE which met the inclusion criteria for the review. Two evidence summary reports published by the Scottish Health Technologies Group (SHTG)[105, 106] did not meet the inclusion criteria as they reported comparative cost analyses; these reports were considered as "near misses" but were included in the review for completeness. No additional studies were identified from handsearching the reference lists of the included studies. A further unpublished manuscript describing a costing analysis of CCE for detecting colorectal polyps and CRC was submitted to NICE by the manufacturer;[107] this study was also considered as a "near miss" and is summarised separately in Section 4.2.

Figure 8: PRISMA diagram for review of existing cost-effectiveness studies



**The searches included the following organisations: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR), European Cancer Summit, Digestive Diseases Week (DDW), United European Gastroenterology Week (UEGW), Asian Pacific Digestive Week (APDW) and the British Society of Gastroenterology Annual Meeting.*
†N includes "near-misses"

4.1.2. Summary and critical appraisal of studies included in the review

The full economic evaluation reported by Palimaka *et al.*[104] is summarised and critically appraised in Section 4.1.2.1. The costing analyses conducted by the SHTG[105, 106] are summarised in Section 4.1.2.2.

4.1.2.1. Palimaka et al. - Colon capsule endoscopy for the detection of colorectal polyps: An economic analysis[104]

Summary of the methods and results reported by Palimaka et al.

Palimaka *et al.*[104] present the methods and results of a model-based cost-effectiveness analysis of CCE using PillCam COLON 2 (Given Imaging Ltd., subsequently acquired by Medtronic Ltd.) versus CTC in adults with known or suspected colonic disease. At model entry, patients are assumed to be 67 years of age, based on data obtained from the Institute for Clinical Evaluative Sciences (ICES) on the number of CTC procedures performed from 2008 to 2012. Cost-effectiveness is reported in terms of the incremental cost per life year gained (LYG) associated with the avoidance of misdiagnoses of colorectal polyps (FP and FN diagnoses). The economic analysis adopted a lifetime horizon and was conducted from the (payer) perspective of the Ontario Ministry of Health and Long-Term Care. Health outcomes and costs were discounted at a rate of 5% per annum. Costs were valued in Canadian Dollars (CAN $) at 2014 prices. The authors also report an accompanying budget impact analysis which estimated the 1-year costs associated with: (i) replacing all CTC procedures in Ontario with CCE or (ii) using CCE instead of CTC in people following an incomplete prior COL.

The cost-effectiveness analysis uses a hybrid modelling approach which included: (i) a short-term decision tree which estimates the probability of a positive or negative diagnostic test result given the patient's true underlying pathology, and (ii) a state transition model which is used to estimate long-term health outcomes and costs for people with an FN test result (individuals in whom polyps are present but are missed by the test). The model structure is restricted to the detection of polyps which are ≥10mm in size; the authors justify the exclusion of <10mm polyps from the model structure on the basis that misdiagnoses of non-advanced polyps would be expected to have only a limited impact in terms of development into larger polyps or CRC. The short-term decision tree model was informed by a prior systematic review of the diagnostic accuracy of CCE using PillCam COLON 2 conducted by Health Quality Ontario.[108] The long-term state transition model was informed by a previous cost-effectiveness model of CRC screening programmes in North America reported by Heitman *et al.*[109] The state transition model includes the following discrete health states: small adenomas; large adenomas; alive after polypectomy; pre-clinical CRC; symptomatic CRC; cancer survival; cancer treatment and dead. The broader hybrid economic model includes costs associated with: (i) the diagnostic tests (CCE and CTC); (ii) complications resulting from the diagnostic tests; (iii) unnecessary COLs for individuals with FP test results and (iv) additional cancer treatment in individuals with FN test results. Complications related to CCE include retention and technical failure of the capsule. Complications related to CTC include perforation due to air insufflation and life years (LYs) lost due to an increased cancer risk resulting from exposure to ionising radiation during the CTC procedure. The model assumes that the prevalence of AAs is 7% within the target population. CCE is assumed to be more sensitive than CTC for detecting AAs (92.8% vs 78.6%); the specificity of the two tests is assumed to be very similar

(91.6% vs 91.7%). Procedure costs, including the costs of managing complications, were estimated to be lower for CTC compared with CCE ($746.20 versus $1,120.42). The base case analysis was based on point estimates of parameters. Uncertainty was assessed using one-way sensitivity analysis and included alternative assumptions regarding: (i) the costs of CCE and CTC; (ii) the costs of managing complications; (iii) the costs of treating CRC; (iv) the sensitivity and specificity of CCE and CTC and (v) the prevalence of AAs.

The results of the base case analysis reported by Palimaka *et al.*[104] are summarised in Table 24. The model suggests that CCE leads to a small incremental gain in survival (0.000966 LYGs) at an additional cost of $258.36 per patient tested. The authors report an incremental cost-effectiveness ratio (ICER) for CCE versus CTC of $26,751 per LYG. The results of the one-way sensitivity analyses suggest ICERs ranging from $6,062 to $196,297 per LYG. Less favourable ICERs for CCE versus CTC were reported for scenarios in which: (i) the sensitivity of CCE was lower than the base case estimate (85.0% vs 92.8%); (ii) the sensitivity of CTC was higher than the base case estimate (90.0% vs 78.6%) and (iii) the prevalence of AAs was assumed to be lower than the base case estimate (3% versus 7%). The authors conclude that the cost-effectiveness of CCE is favourable compared with CTC, but that there is uncertainty due to the lack of a statistically significant difference in the diagnostic accuracy of CCE versus CTC in detecting ≥10mm polyps. The authors highlight that the ICER for CCE versus CTC is highly sensitive to changes in assumptions regarding the sensitivity of the two diagnostic tests.

Table 24: Base case cost-effectiveness results for CCE versus CTC (values as reported by Palimaka *et al.*), CAN $

Option	LYGs by avoiding FNs	Total cost (test cost + FN cost + FP cost)	ICER (incremental cost per LYG)
CCE	NR	$862.47	-
CTC	NR	$1,120.83	-
Incremental	0.000966	$258.36	**$26,751***

CCE - colon capsule endoscopy; CTC - computed tomography colonography; LYG - life year gained; FN - false-negative; FP - false-positive; ICER - incremental cost-effectiveness ratio; CAN - Canadian
** The EAG notes that dividing the incremental costs by the incremental LYGs shown in this table does not produce the ICER reported by Palimaka et al. The reasons for this are unclear.*

The budget impact analysis found that CCE was expected to be cost-incurring compared with CTC, regardless of whether the test is used to replace all CTCs, or only those CTCs undertaken in patients with a prior incomplete COL.

Key issues identified from the critical appraisal of Palimaka et al.

The EAG critically appraised the economic analysis reported by Palimaka *et al.*[104] based on the key items listed in Weinstein *et al*.[110] The general hybrid modelling approach reported by Palimaka *et al.* appears to be appropriate given the decision problem, and the use of a previous systematic review of diagnostic accuracy[108] to inform the model parameters is a strength of the analysis. However, the EAG has several concerns with the reported economic analysis:

- The economic model structure focusses only on the detection of ≥10mm polyps. If the diagnostic accuracy of CCE and CTC in detecting smaller polyps differs between the tests, and if further intervention would subsequently be required to remove those polyps upon detection, the exclusion of small polyps from the model structure may produce misleading results.
- The model does not include CRC as a possible underlying pathology detected by CCE or CTC. The reasons for this exclusion are unclear, as the stated research objectives included assessing the impact of CCE for detecting both adenomas and CRC. The exclusion of CRC from the model structure implicitly assumes that CTC and CCE have identical test characteristics for detecting CRC. Even if this assumption was considered to be clinically plausible, it would have been preferable to include CRC as part of the model structure and to test the assumption of equivalent diagnostic accuracy between the tests in sensitivity analyses.
- Health outcomes are restricted to differences in survival due to FN diagnoses. This approach ignores any differential impacts of test-related complications, the disease or any subsequent treatment on HRQoL.
- The cost estimates included in the economic analyses do not appear to include any subsequent costs of follow-up procedures for people with a TP test result. Given that the sensitivities of CCE and CTC are assumed to differ, it is likely that the expected costs of subsequent interventions required to remove detected polyps would also differ.
- The model includes a CCE failure probability of 1.4%; [redacted]

  Incomplete CCE would likely require further investigations which would increase costs for the CCE group.
- The authors report a base case ICER for CCE versus CTC of CAN $26,751 per LYG. However, based on the incremental LYGs and incremental costs reported in Table 24, which have been reproduced from Table 9 of the paper by Palimaka *et al.*,[104] the ICER for CCE versus CTC is substantially higher at around CAN $267,000 per LYG. The EAG believes that this discrepancy is likely to be a typographical error in the incremental LYGs reported in the paper, but alternatively, it is possible that the ICER has been miscalculated. If the latter explanation

applies, this would suggest that CCE has a substantially less favourable cost-effectiveness profile than that suggested by Palimaka *et al.*[104]

- The economic analysis is restricted to a comparison of CCE versus CTC; a comparison of CCE versus COL is not presented.
- All analyses presented are deterministic in nature. Probabilistic sensitivity analysis (PSA) is not presented.

4.1.2.2. SHTG 2020 evidence summary[105] and 2024 updated evidence summary[106]

Summary of the methods and results of the SHTG costing analyses

In 2020, the SHTG published a report summarising the available clinical and economic evidence for the use of second-generation CCE for detecting colorectal polyps.[105] In 2024, the SHTG published an updated Innovative Medical Technology Overview (IMTO) on the use of second-generation CCE for detecting colorectal polyps and cancer.[106] The 2020 SHTG report included a comparative cost analysis of CCE delivered locally (from regional hubs) versus the current COL-based diagnostic pathway in Scotland, using data from a CCE registry established as part of the ScotCap programme.[31] This cost analysis was updated in the 2024 SHTG report. The updated 2024 cost analysis is described below.

The costing analysis included costs borne by NHS Scotland only. The data included in the updated cost analysis related to patients who had a CCE after bowel preparation using prucalopride was introduced into the ScotCap programme to improve CCE completion rates (between May to October 2023) up to the data cut-off (November 2023). The analysis assumes that there is no difference in diagnostic test accuracy or health outcomes for CCE versus the current COL-based diagnostic pathway. The total cost per CCE procedure was assumed to be £747 at its list price based on a micro-costing exercise, whereas the total cost per COL was estimated to be £900. Other model parameters were taken from ScotCap, the Scottish BCSP, the manufacturer of PillCam COLON 2 (Medtronic Ltd.), routine cost sources, literature and expert opinion.

Within the updated 2024 analysis,[106] cost comparisons of CCE versus the current COL-based diagnostic pathway were conducted for three populations which broadly align with the populations listed in the final NICE scope for the current appraisal:[35] (i) people undergoing post-polypectomy surveillance; (ii) people with CRC symptoms and a positive FIT, and (iii) people with CRC symptoms and a negative FIT (the FIT cut-off was not defined in the SHTG report). The updated 2024 costing analysis suggested the following conclusions:

(i) Compared with the current COL-based diagnostic pathway, CCE is cost-incurring in the surveillance population (additional cost per patient = £64.75).
(ii) Compared with the current COL-based diagnostic pathway, CCE is marginally cost-saving in both symptomatic populations (cost savings per patient of £6.71 in the FIT positive population and £0.36 in the FIT negative population).

The updated 2024 SHTG report[106] states that the difference in estimated costs between the surveillance and symptomatic populations is driven by a higher proportion of symptomatic patients who undergo CCE and subsequently receive FSIG as a subsequent procedure instead of COL (the latter test being more expensive than the former). The precise assumptions and parameter values adopted in the udpated cost analysis are not included in the 2024 SHTG report.[106] As such, the EAG is unable to provide a detailed critique of the analysis.

4.2. Review of manufacturer's submitted model

4.2.1. Medtronic - Colon capsule endoscopy as a colonoscopy sparing diagnostic in people with suspected colorectal cancer: A UK cost comparison and system benefits analysis (unpublished manuscript submitted to NICE)[107]

In September 2024, the manufacturer of PillCam COLON 2 (Medtronic Ltd.) submitted an unpublished manuscript to NICE which reports on the methods and results of a *de novo* model-based cost comparison and resource use analysis of CCE testing for people with symptoms of CRC who are referred to secondary care with a FIT score of 10-100µg/g.[107] A supplementary appendix containing further details regarding the model inputs and the results of additional sensitivity analyses was also provided. The executable model described in the manuscript was not made available to the EAG for scrutiny. As noted in Section 4.1, this costing study did not meet the inclusion criteria for the EAG's review as it is not a full economic evaluation; however, the study was summarised and critically appraised for completeness.

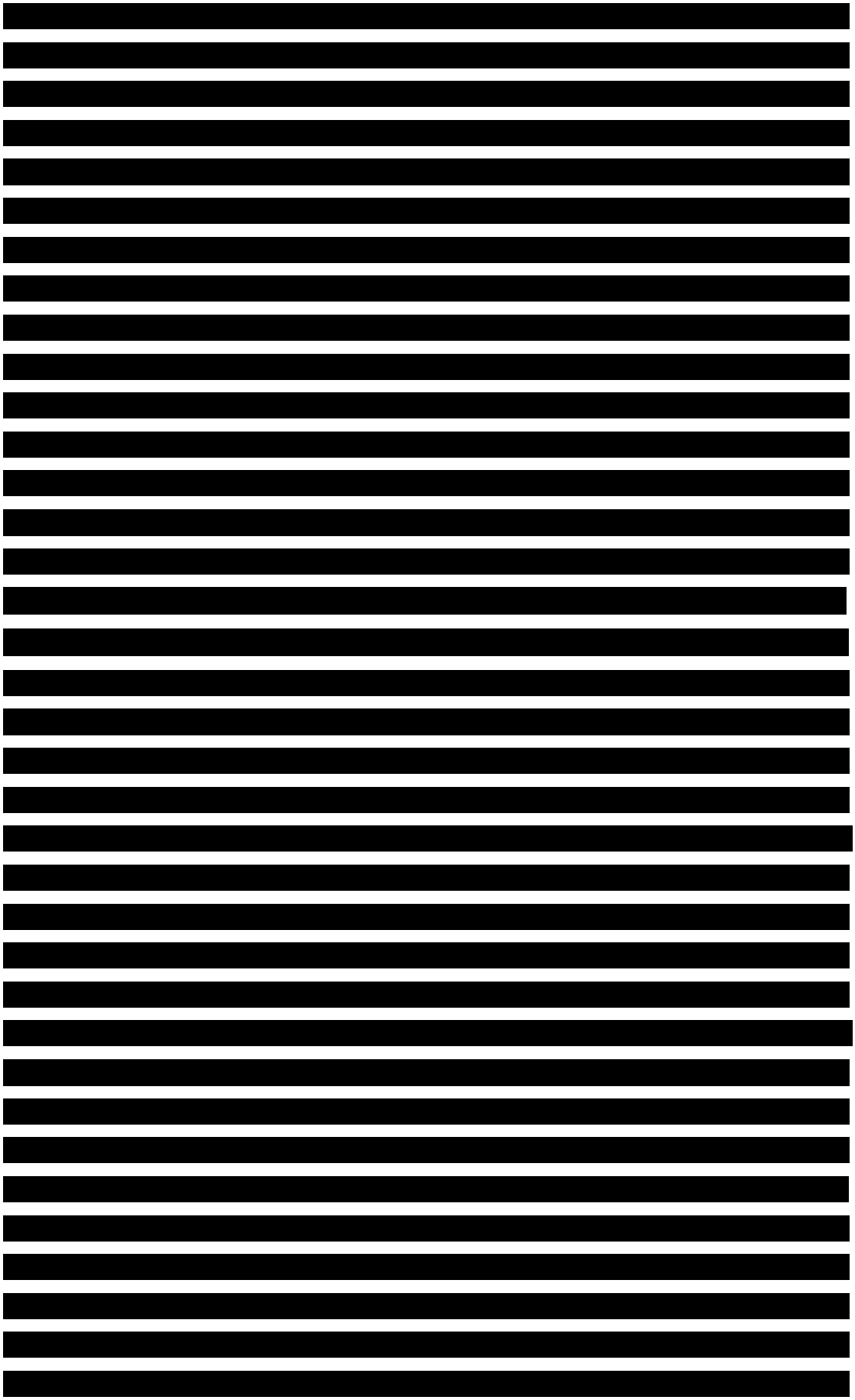
[redacted]

[redacted]

Table 25: Assumed sensitivity of CCE, COL and CTC in the company's costing model

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]



[redacted]

[redacted]

4.3. Independent EAG economic analysis

4.3.1. Scope of the EAG's economic analysis

The EAG developed a *de novo* health economic model to assess the incremental cost-effectiveness of CCE versus COL and CTC. The scope of the EAG's model is summarised in Table 26. The model assesses the health outcomes and costs of each diagnostic testing strategy from the perspective of the NHS and PSS over a lifetime horizon (up to a maximum patient age of 100 years). All health outcomes and costs are discounted at a rate of 3.5% per annum.[119] The economic analysis adopts a formal price year of 2022/23 (except for CCE device costs which are valued at current prices provided by the manufacturer), including uplifting of older cost estimates using inflation indices,[120, 121] where necessary.

Table 26: Scope of the EAG economic analysis

Population*	(1) Adults with lower GI signs or symptoms suggestive of CRC who are referred to secondary care. Subgroups for this population include: • People with a FIT score of 10-100µg/g • People with a FIT score of <10µg/g with concerning clinical symptoms. (2) Adults who are due to have a post-polypectomy surveillance COL at 3-years because of high-risk findings at their baseline COL. Within each population, the model includes consideration of: • People who have declined COL • People who have had an incomplete index diagnostic test (COL, CCE or CTC) despite adequate bowel preparation.
Intervention	PillCam COLON 2 (CCE)
Comparators	• COL • CTC
Main economic outcome	Incremental cost per QALY gained
Additional model outcomes	• Incremental LYGs • Incremental QALYs gained • Incremental costs • Reduction in the number of COLs/FSIGs • Proportion of people requiring follow-up COL/FSIG • Number of polyps detected and missed

	• Number of cancers detected and missed • Number of IBDs detected and missed • Morbidity and mortality associated with complications.
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per annum
Price year	2022/2023

FIT - faecal immunochemical test; GI - gastrointestinal; CRC - colorectal cancer; LYG - life year gained; QALY - quality-adjusted life year; IBD - inflammatory bowel disease; COL - colonoscopy; FSIG - flexible sigmoidoscopy; CTC - computed tomography colonography; CCE - colon capsule endoscopy; NHS - National Health Service; PSS - Personal Social Services
** Based on clinical advice, people with a rectal or anal mass or anal ulceration ("bypass symptoms") were excluded from the scope of the appraisal and therefore are not considered in the model populations.*

4.3.1.1. Population

Overall, the population reflected in the economic model relates to: (i) adults with lower GI signs or symptoms suggestive of CRC who are referred to secondary care, and (ii) adults who are due to have a post-polypectomy surveillance COL at 3-years following the identification of high-risk findings at their baseline COL. In line with the design of the NHSE CCE Pilot Study,[32] the population with lower GI signs and symptoms is further sub-divided into two groups according to the patient's FIT score: (a) people with symptoms suggestive of CRC with a FIT score of 10-100μg/g, and (b) people with concerning symptoms suggestive of CRC with a FIT score of <10μg/g. Therefore, the economic analysis includes three main populations; this is in line with the final NICE scope.[35] People with a FIT score of >100μg/g are high-risk and would be expected to undergo a COL; these patients are therefore not included in the economic analysis.

The final NICE scope[35] includes the consideration of two subgroups within these three main populations: (i) people who have an incomplete index diagnostic test despite adequate bowel preparation (incomplete COL is mentioned specifically in the scope, although CCE and CTC may also be incomplete), and (ii) people who have declined COL. The probability that the first (index) test received is incomplete is reflected in the diagnostic pathways included in the economic model in all analysis populations. The possibility that individuals are unwilling to undergo COL is handled through subgroup analyses, whereby the model includes alternative diagnostic pathways and comparator tests between patients who opt to undergo COL and patients who decline COL. The EAG's clinical advisors highlighted that, in practice, most patients who are initially unwilling to undergo COL may be persuaded to undergo this procedure where it is clinically indicated (e.g., if an alternative prior index test indicates the presence of significant underlying bowel pathology and subsequent biopsy or polypectomy is needed). Therefore, the model assumes that people who initially decline COL and in whom significant bowel pathology is detected through other luminal investigations (e.g., CTC or CCE) will later undergo COL or FSIG in order for a biopsy or polypectomy to be undertaken. Patients who are initially willing

to undergo COL and those who initially decline COL are hereafter referred to as "COL-eligible" and "COL-ineligible", respectively.

The use of CCE in older or frail patients who are unfit for COL or surgery is excluded from the economic analysis. This is because polypectomy and/or biopsy will not be possible for these patients and any identified polyps or CRC would necessarily be left *in situ*. CCE is likely to be of limited clinical value for these patients due to the burden of bowel preparation and additional booster medicines relative to other investigations (such as CTC or CT).

4.3.1.2 Intervention

The intervention included in the model is PillCam COLON 2. The intervention is assumed to be swallowed by the patient under supervision by a health care professional in an outpatient setting and the transmitted data are assumed to be read by a trained endoscopist. The base case economic analysis excludes the costs of patency capsules administered prior to the CCE to mitigate the risks of capsule retention, but includes the costs of an abdominal X-ray for a proportion of patients with an incomplete CCE who do not report excretion of the capsule and the costs of a CT scan for those patients with confirmed retention. The use of PillCam patency capsules and supervised swallowing of the capsule in a primary care setting are explored as part of the EAG's scenario analyses (see Section 4.3.6.4).

For brevity, PillCam COLON 2 is hereafter referred to as "CCE" throughout the remainder of this chapter.

4.3.1.3. Comparator

For the COL-eligible population, the model includes two comparators: (i) COL and (ii) CTC. For patients who are initially unwilling to undergo COL, CTC is the only comparator; however, as noted in Section 4.3.1.1, the model assumes that these patients will eventually undergo a COL (or FSIG) if significant bowel pathology is identified using other tests and polypectomy or biopsy is needed.

4.3.1.4. Summary of interventions and comparators by population

Table 27 summarises the populations, interventions and comparators included in the EAG's economic analyses.

Table 27: Summary of the EAG's economic comparisons by subgroup

Analysis No.	Population	COL-eligible?	Intervention	Comparators
1a	Symptomatic, FIT 10-100µg/g	Yes	CCE	COL, CTC
1b		No	CCE	CTC
2a	Symptomatic, FIT <10µg/g	Yes	CCE	COL, CTC
2b		No	CCE	CTC
3a		Yes	CCE	COL, CTC

3b	Surveillance (post-polypectomy)	No	CCE	CTC

COL - colonoscopy; CCE - colon capsule endoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test

4.3.2. Model structure and assumptions

4.3.2.1. Overview of the EAG's model

This section describes the structure of the EAG's model. The model structure was developed through consultation with three clinical experts (MK, KM and JT) and through consideration of previous models of CCE for detecting colorectal polyps and CRC.[104, 107] The general structure of the EAG's economic model is shown in Figure 9. The model consists of: (i) a short-term decision tree which is used to model the diagnostic pathways and outcomes for adults with lower GI signs or symptoms suggestive of CRC, or for those who are due to have their 3-year post-polypectomy surveillance test, and (ii) a long-term model which is used to estimate expected lifetime health outcomes and costs according to the patient's true underlying pathology and the test findings at the point of the index test. As described in Section 4.3.1, three main analysis populations are considered in the model: (1) symptomatic patients with a FIT score of 10-100µg/g; (2) symptomatic patients with a FIT score of <10µg/g and (3) patients who are due to have a post-polypectomy surveillance test at 3-years because of high-risk findings at their baseline COL. In each of these three populations, the model defines the patient's true underlying pathology at the time of the index test in terms of the presence of: (i) CRC; (ii) AAs; (iii) low-risk adenomas (LRAs) or (iv) IBD. Patients without CRC, polyps or IBD are classed as having no significant bowel pathology (NSBP). The model assumes that these groups are mutually exclusive and jointly exhaustive, with membership of each group determined by the most advanced colorectal pathology present (e.g., if a patient has both CRC and AAs, they would fall into the CRC group).

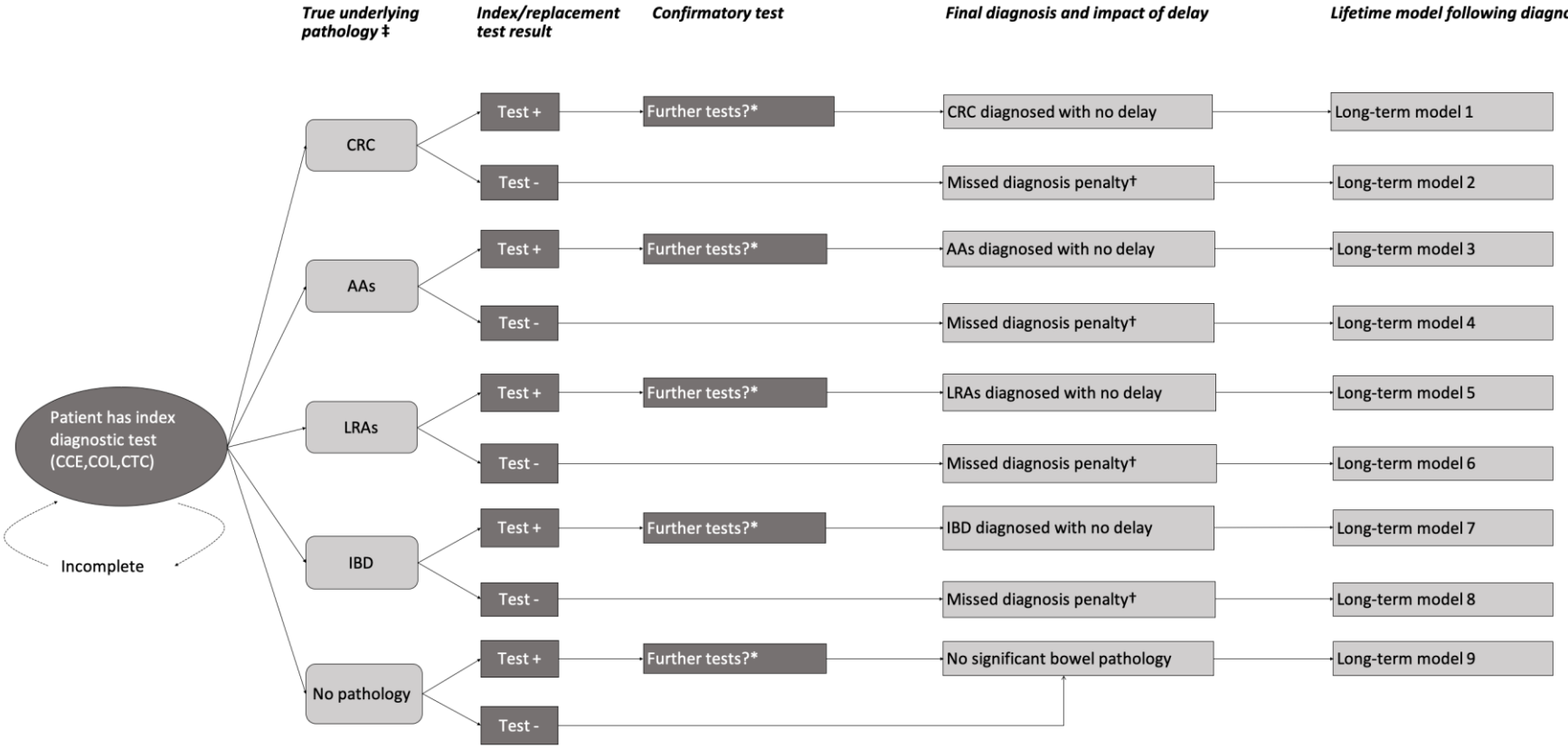
The model is intended to reflect the use of the diagnostic tests in three situations, which are defined as follows:

(a) Index tests – this is the first diagnostic test that the patient is referred for.
(b) Replacement tests – these tests are used in place of the index test if it fails for any reason.
(c) Confirmatory tests – these tests are used to confirm positive findings indicated by the index or replacement test.

The general structure of the economic model is the same for all three populations. The model assumes that the prevalence of each underlying bowel pathology (CRC, AAs, LRAs and IBD) differs between each of the three main populations, whereas the initial diagnostic pathways (i.e., the index tests available and the replacement tests used in cases where the index test is incomplete) also differ between patients who are COL-eligible or COL-ineligible. The model combines information on the prevalence of each pathology, diagnostic accuracy, harms and costs for each test and the long-term health outcomes and

costs conditional on each pathology group and test results to estimate lifetime survival, QALYs and costs for each diagnostic testing strategy. In instances in which significant bowel pathology is missed by the index test (or if the index test is incomplete, the replacement test), the model includes penalties associated with misdiagnosis which impact on long-term QALY gains and costs. These penalties are intended to reflect the impact of a stage-shift in CRC, the risk of increased growth or malignant transformation of adenomas or increased severity of non-malignant IBD resulting from a diagnostic delay.

Figure 9: General structure of the EAG model (short- and long-term models)



COL - colonoscopy; CTC - computed tomography colonography; CCE - colon capsule endoscopy; CRC - colorectal cancer; LRA - low-risk adenomas; AAs - advanced adenomas; IBD - inflammatory bowel disease

** Following a positive index test, the further tests required will depend on the acceptability of COL and the pathology detected. This may include diagnostic or therapeutic COL (or in some patients, FSIG).*

† For patients with underlying CRC, this penalty is estimated as a potential worsening shift in cancer stage. For people with AAs and LRAs, a penalty is applied to reflect an increased risk of polyp growth or progression to CRC. For people with IBD, a penalty is applied to reflect potential worsening of disease severity at the point of later diagnosis.

‡ The prevalence of each bowel pathology differs between the populations listed in the NICE scope.

The index test is an intervention or a comparator listed in the final NICE scope (CCE, COL or CTC). A replacement test is a diagnostic test which is used to replace an incomplete index test, and it may be the same as the index test or a different comparator test, depending on the reason for the index test being incomplete and COL-eligibility. A completed index test or replacement test will give an initial diagnosis. The further tests reflect confirmatory tests which will ultimately provide the correct diagnosis of the underlying bowel pathology, where present.

4.3.2.2. Short-term decision tree structure

The decision tree component of the model has a short time horizon and is intended to represent the whole diagnostic pathway starting from the time point at which the index test (COL, CTC or CCE) is performed through to the time point at which a final correct diagnosis is reached. The structure of the decision tree for the intervention and comparator groups differs between patients who are COL-eligible and those who are COL-ineligible because COL can only be used as an index or replacement test in people who are willing and able to undergo this procedure (see Figure 10 and Figure 11). The decision tree estimates the expected probability of identifying CRC, LRAs, AAs, IBD and NSBP for each testing strategy (CCE, CTC and COL, where applicable). The model assumes that for each testing strategy, a proportion of index tests will be incomplete, either because of inadequate bowel preparation or due to other causes despite adequate bowel preparation (e.g., bowel stricture, obstruction or patient discomfort). For COL, if the index test is incomplete due to inadequate bowel preparation, patients are assumed to undergo a repeat COL at a later date. If COL is incomplete due to other reasons (e.g., due to stricture or patient discomfort), most patients are assumed to undergo a different replacement test, although some will go on to have a repeat COL. For CCE and CTC, if the index test is incomplete, the model assumes that an alternative test will be offered (COL or FSIG where possible), regardless of the reason for incompletion. The choice of replacement test is assumed to be dependent on whether the patient is COL-eligible (see Table 28). Incomplete index COL is assumed to provide no diagnostic information, whereas incomplete CTC and CCE may be partially diagnostic, allowing subsequent tests to be limited to examination of the distal colon using FSIG rather than COL, where appropriate. The full costs and risks of complications of all incomplete tests are assumed to be incurred. The replacement test is assumed to be performed at a separate appointment from the index test. The replacement test is assumed to be complete in every case, provides diagnostic information and also carries a risk of complications.

Table 28: Assumed replacement tests used following an incomplete index test

Intervention/ comparator group	COL eligibility	Index test	Replacement test if index test is incomplete due to inadequate bowel preparation	Replacement test if the index test is incomplete despite adequate bowel preparation
CCE†	COL-eligible	CCE	COL	COL
	COL-ineligible	CCE	CTC	CTC
COL	COL-eligible	COL	COL	CTC or COL*
	COL-ineligible	N/a	N/a	N/a
CTC†	COL-eligible	CTC	COL	COL
	COL-ineligible	CTC	CCE‡	CCE‡

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; N/a - not applicable

** Some patients in whom the index COL is incomplete for reasons other than inadequate bowel preparation (e.g., patient discomfort) are assumed to undergo a repeat COL*

†The model assumes that following incomplete CCE and CTC, FSIG rather than COL may be used as a replacement test in some patients

‡The use of non-invasive tests instead of CCE is explored in sensitivity analyses (DSA25)

Patients who have a TP result for significant bowel pathology (LRAs, AAs, CRC or IBD) at the index or replacement test are assumed to be referred for a confirmatory test in secondary care (see Table 29). Confirmatory tests could be either diagnostic or therapeutic COL or FSIG. Patients with NSBP who test positive at the index or replacement test (i.e., FPs) are assumed to be referred on for a confirmatory diagnostic COL/FSIG which will ultimately lead to a correct diagnosis and the patient will subsequently be discharged. These individuals are assumed to incur additional short-term testing costs but do not incur any long-term costs or QALY losses. People with polyps who have a complete COL/FSIG as an index/replacement test are assumed to undergo polypectomy as part of the procedure, or where necessary (e.g., in the case of "complex polyps"), during a subsequent COL/FSIG procedure (see Section 4.3.2.4). After being correctly diagnosed by the confirmatory COL/FSIG (where indicated), patients with a TP result for underlying CRC, polyps or IBD are assigned the payoffs from the long-term model (see details in Section 4.3.2.3).

People who test negative with the index/replacement test are assumed not to be offered a confirmatory test immediately. People with NSBP who test negative (TNs) are assumed to be discharged immediately and incur no further costs; these patients have the same outcomes as the general population. Patients with significant underlying bowel pathology who are missed by the testing strategy (FNs) are assumed to eventually be correctly diagnosed either through later presentation to their General Practitioner (GP) or through presentation to Accident and Emergency (A&E) with late signs or symptoms. The long-term model payoffs for these individuals include a delay in the time to reach the correct diagnosis of CRC, adenomas, or IBD which acts as a penalty on the QALYs accrued by the patient and the costs incurred by the health service. Time to diagnosis is assumed to include the time at which the index test is performed in secondary care to the time point at which the correct final diagnosis is obtained.

The decision tree model includes risks of complications for all index, replacement and confirmatory tests. For COL/FSIG, the model includes risks associated with bleeding, perforation and death. For CTC, the model includes risks associated with perforation caused by air insufflation and exposure to ionising radiation which increases the lifetime risk of developing CRC. For CCE, the model includes risks associated with capsule aspiration and retention. Each of these complications is assumed to incur an additional cost and all complications except for capsule aspiration are assumed to result in QALY losses. Patients who die as a consequence of complications of the index, replacement or confirmatory test are not assigned QALYs or costs from the long-term model.

Table 29: Subsequent confirmatory tests for positive cases identified by the index or replacement test

Index or replacement test	Underlying pathology	Assumed confirmatory test†
CCE	CRC	COL (diagnostic)
	AAs	COL (therapeutic)
	LRAs	COL (therapeutic)
	IBD	COL (diagnostic)
CTC	CRC	COL (diagnostic)
	AAs	COL (therapeutic)
	LRAs	COL (therapeutic)
	IBD	COL (diagnostic)
COL	CRC	None
	AAs	COL (therapeutic)‡
	LRAs	None§
	IBD	None

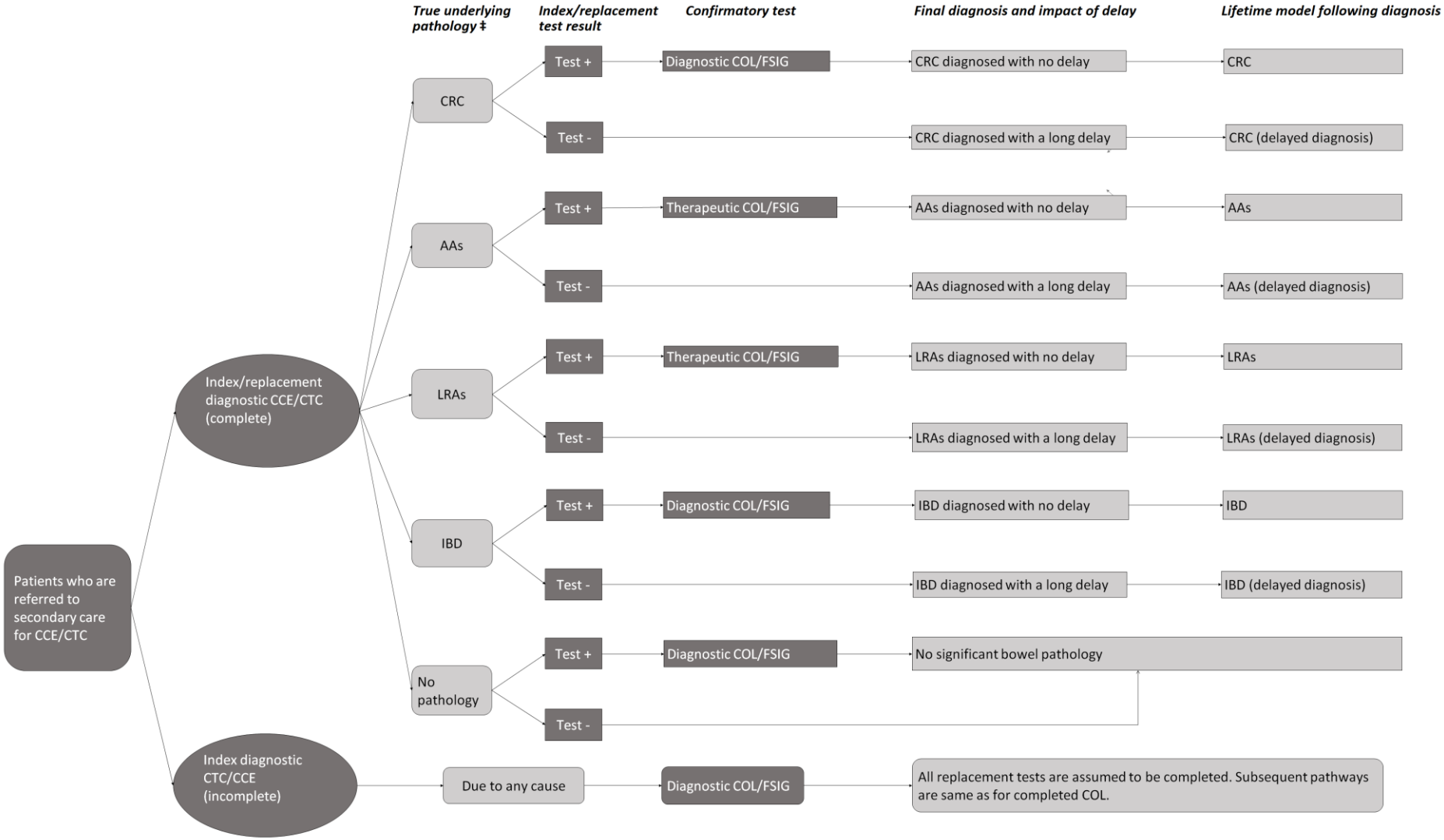
COL - colonoscopy; CCE - colon capsule endoscopy; CTC - computed tomography colonography; CRC - colorectal cancer; AA - advanced adenoma; LRA - low-risk adenoma; IBD - inflammatory bowel disease; endoscopic mucosal resection

† The model assumes that a proportion of patients undergo FSIG rather than COL as a confirmatory test (i.e., where a prior complete index/replacement test indicates that any relevant bowel pathology is limited to the distal portion of the colon)

‡ 10% of polyps are assumed to be complex and require a second endoscopy procedure e.g., EMR

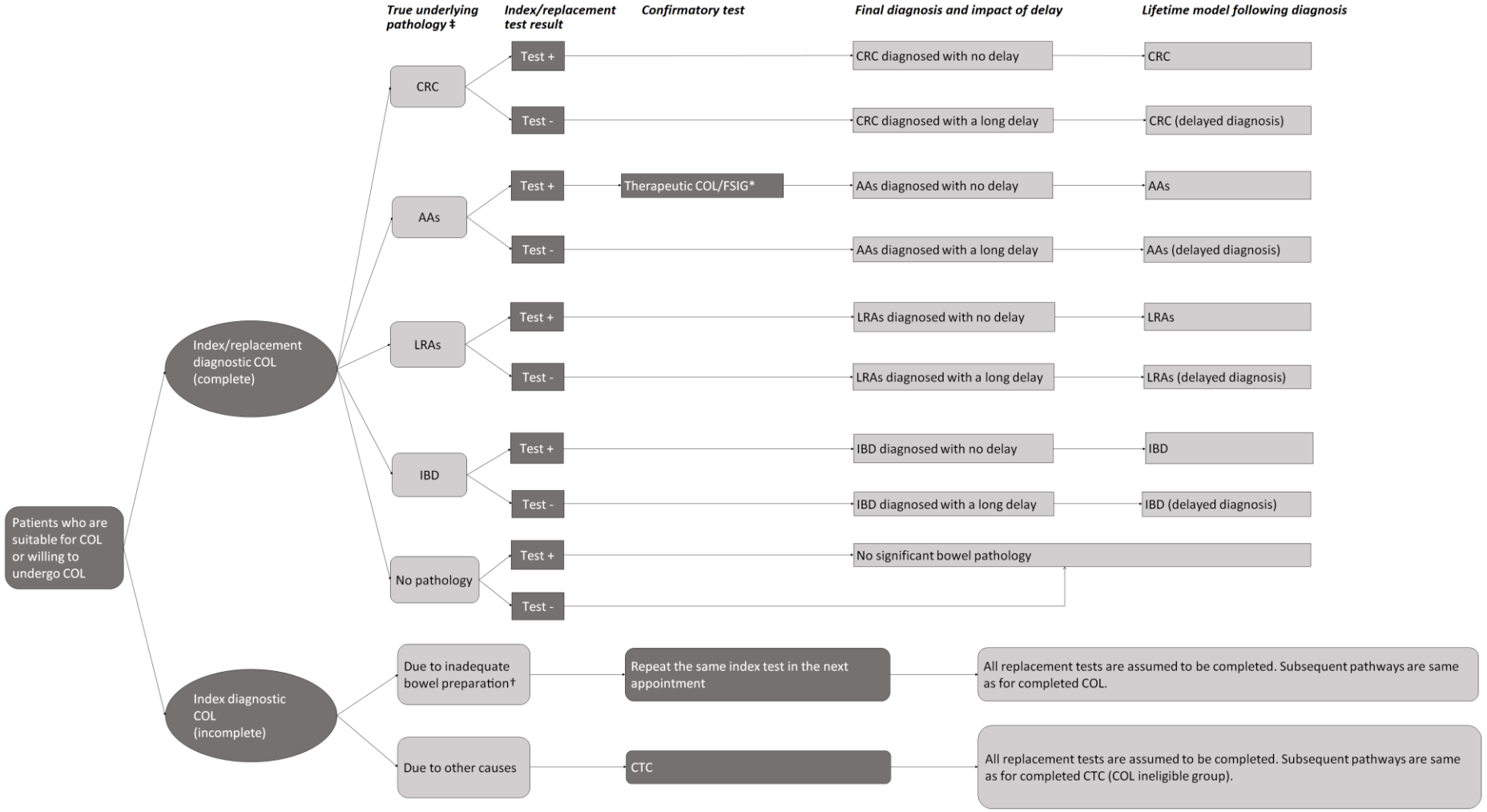
§ The model assumes that all LRAs can be removed immediately at the index or replacement COL/FSIG. Therefore, no additional confirmatory test is required for these patients.

Figure 10: Decision tree structure for CCE and CTC



COL - colonoscopy; CTC - computed colonography; CCE - colon capsule endoscopy; FSIG - flexible sigmoidoscopy; CRC - colorectal cancer; LRAs - low-risk adenomas; AAs - advanced adenomas; IBD - inflammatory bowel disease

Figure 11: Decision tree structure for COL



COL - colonoscopy; CTC - computed colonography; CCE - colon capsule endoscopy; FSIG - flexible sigmoidoscopy; CRC - colorectal cancer; LRAs - low-risk adenomas; AAs - advanced adenomas; IBD - inflammatory bowel disease
** 10% of AAs assumed to require therapeutic COL/FSIG to remove complex polyps*
†The model assumes that some patients with an incomplete COL will undergo a further COL rather than switching to a different test.

4.3.2.3. Long-term model outcomes

Mean LYGs, QALYs and costs for each testing strategy are calculated within the EAG's model by multiplying the expected probabilities derived from the decision tree by the lifetime LYGs, QALYs and costs associated with a diagnosis of each pathology, with or without a diagnostic delay. For patients with CRC, AAs or LRAs, lifetime health outcomes and costs are based on re-analyses of the MiMiC-Bowel CRC screening model (see Appendix 7).[111, 122] For people with IBD or NSBP, lifetime health outcomes and costs are based on separate quality-adjusted survival models based on general population life expectancy tables.[123] This approach is similar to the approach taken in the model developed to inform the NICE appraisal of quantitative FIT to guide CRC pathway referral in primary care (DG56).[23]

Long-term models 1-4 (CRC and AAs with and without additional diagnostic delays)

For symptomatic patients with underlying CRC or AAs (Figure 9, long-term models 1-4), lifetime payoffs (LYGs, QALYs and costs) were informed by an economic analysis exploring the impact of additional delays in the diagnosis of AAs or CRC on health outcomes and costs, undertaken using the MiMiC-Bowel model (Whyte *et al.*[122]). This is an updated version of the analysis that was used to inform DG56.[23] The analysis by Whyte *et al.* combines information on AA prevalence and CRC stage at the point of diagnosis under the 2WW referral system,[124] the risks of malignant transformation of undiagnosed AAs and CRC progression over time, and estimated LYGs, QALYs and health care costs for people with AAs and CRC (defined in terms of Dukes' Stages A-C and Stage D).[125] For people who are diagnosed with CRC without an additional diagnostic delay (Figure 9, long-term model 1), lifetime LYGs, QALYs and costs by CRC stage from MiMiC-Bowel were applied to the 2WW distribution of CRC stage at diagnosis.[124] People with AAs who are diagnosed without an additional diagnostic delay (Figure 9, long-term model 3) are assumed to undergo polypectomy and have the same health outcomes as the general population.[123, 126] Within the long-term models for people who are diagnosed with CRC or AAs following a diagnostic delay (Figure 9, long-term models 2 and 4), the CRC stage distribution at diagnosis was re-estimated using transition probabilities taken from MiMiC-Bowel to take into account expected adenoma progression and/or CRC stage-shift over the duration of the additional delay. Lifetime LYGs, QALYs and costs by stage were then applied to this updated stage distribution including the impact of the delay. The EAG's base case model assumes that the average length of the delay in correcting a misdiagnosis is 8 months for CRC and 36 months for polyps. These estimates were informed by input received from the EAG's clinical advisors, with the estimate for polyps based on the maximum value reported by Whyte *et al*.

Within the post-polypectomy surveillance population, lifetime payoffs were informed by separate re-analyses conducted using the MiMiC-Bowel model.[125] Within these analyses, all patients enter the MiMiC-Bowel model with either undiagnosed CRC (Dukes' Stages A-C or Stage D) or AAs (following polypectomy) and are assumed to undergo a surveillance test in the first year of the simulation; this test is assumed to have either 100% sensitivity or 0% sensitivity (either the patient's true underlying

pathology is detected without delay or is missed and later diagnosed with delay). Lifetime payoffs for patients with AAs were applied directly to the expected probabilities in the decision tree (Figure 9, long-term models 3 and 4). Lifetime payoffs for patients with CRC were weighted assuming a 50:50 split between Dukes' stages A and B and were then applied to the expected probabilities in the decision tree (Figure 9, long-term models 1 and 2). It should be noted that this analysis is limited in that only the first test is replaced by CCE; subsequent scheduled luminal investigations for people who remain under surveillance due to the detection of high-risk findings at the 3-year visit are assumed to be done using COL.

Long-term models 5 and 6 (LRAs with and without diagnostic delay)

Estimates of lifetime health outcomes and costs for symptomatic patients with LRAs were not available from the analysis reported by Whyte *et al.*[122] Within the symptomatic population, long-term outcomes for people with LRAs detected without diagnostic delay (Figure 9, long-term model 5) are based on quality-adjusted general population life tables.[123, 126] No additional treatment costs are included for these patients. Survival losses, QALY losses and additional costs associated with missed LRAs in the symptomatic population (Figure 9, long-term model 6) were assumed to be proportional to the ratio of the payoffs for missed diagnoses of LRAs versus AAs in the surveillance population.

Estimates of lifetime health outcomes and costs for patients with LRAs in the surveillance population with or without diagnostic delay (Figure 9, long-term models 5 and 6) were estimated from re-analyses of the MiMiC-Bowel model.[125] Within these analyses, all patients enter the model with LRAs (following polypectomy) and undergo a surveillance test in the first year of the simulation; this test is assumed to have either 100% sensitivity or 0% sensitivity (either the LRAs are detected without delay or are missed at the first test and diagnosed after a delay). Lifetime payoffs for the LRA group were then applied directly to the expected probabilities in the decision tree (Figure 9, long-term models 5 and 6).

Long-term models 7, 8 and 9 (IBD with or without diagnostic delay and NSBP)

For people with IBD or NSBP (Figure 9, long-term models 7, 8 and 9), expected survival is assumed to be equivalent to that of the general population in England.[123] For people with IBD who are diagnosed without a delay (Figure 9, long-term model 7), the model applies an IBD-related utility value and cost in each year that the patient remains alive. People who are diagnosed with IBD following a diagnostic delay (Figure 9, long-term model 8) are assumed to have an additional risk of IBD-related complications, which in turn, leads to lower HRQoL and higher treatment costs for a period of 2 years, based on the same assumptions as those applied in the model used to inform DG56.[127] People who have NSBP (Figure 9, long-term model 9) are assumed to have the same level of HRQoL as the general population[126] and do not incur any subsequent treatment costs. The same approach is applied to patients with NSBP in the symptomatic and surveillance populations.

Table 30 summarises the approach used to estimate long-term outcomes and costs.

Table 30: Summary of lifetime survival, QALYs and costs applied in the long-term models

Payoff	True underlying pathology and final (correct) diagnosis	Source of lifetime outcomes with or without delayed diagnosis
Long-term models 1 and 3	CRC or AAs, no diagnostic delay	*Symptomatic populations (FIT 10-100µg/g and FIT <10µg/g)* Based on Whyte *et al.*[122] Lifetime outcomes predicted for people with CRC based on MiMiC-Bowel,[125] weighted by 2WW CRC distribution.[124] People with AAs assumed to have general population survival and HRQoL following polypectomy.[123, 126] *Surveillance population* Re-analysis of MiMiC-Bowel[125] assuming all patients enter the model with AAs or in CRC states. CRC stage distribution assumed to be 50:50 Dukes' A and Dukes' B.
Long-term models 2 and 4	CRC or AAs, with diagnostic delay	*Symptomatic populations (FIT 10-100µg/g and FIT <10µg/g)* Based on Whyte *et al.*[122] Lifetime outcomes predicted for people with AAs and CRC based on MiMiC-Bowel,[125] weighted by 2WW stage distribution[124] plus modelled progression of AAs and cancer stage-shift due to diagnostic delay. *Surveillance population* Re-analysis of MiMiC-Bowel[125] assuming all patients enter the model with AAs or in CRC states. Impact of diagnostic delay reflected in proportion of patients missed by first post-polypectomy surveillance test.
Long-term models 5 and 6	LRAs, with and without diagnostic delay	*Symptomatic populations (FIT 10-100µg/g and FIT <10µg/g)* People with detected LRAs assumed to have general population survival and HRQoL. Survival losses, QALY losses and additional costs of missed diagnoses of LRAs assumed to be proportional to ratio of payoffs for missed diagnoses of LRAs vs AAs in surveillance population. *Surveillance population* Re-analysis of MiMiC-Bowel[125] assuming all patients enter model with LRAs following polypectomy. Impact of diagnostic delay reflected in proportion of patients missed by first post-polypectomy surveillance test.
Long-term models 7 and 8	IBD, with and without diagnostic delay	*All populations* People with IBD assumed to have general population survival, IBD-related utility and IBD-related treatment costs, based on same assumptions as DG56 model.[127] QALY losses and costs associated with missed diagnosis of IBD also based on DG56 model.[127]
Long-term model 9	No significant bowel pathology	*All populations* People with NSBP assumed to have general population survival and utility. No further costs assumed.

CRC - colorectal cancer; LRAs - low-risk adenomas, AAs - advanced adenomas, IBD - inflammatory bowel disease; MiMiC-Bowel - Microsimulation Model in Cancer of the Bowel; NSBP - no significant bowel pathology; DG - Diagnostics Guidance; 2WW - Two Week Wait; HRQoL - health-related quality of life; FIT - faecal immunochemical test

4.3.2.4. Key structural assumptions

The model employs the following structural assumptions:

- The model begins at the point at which the index test would be performed in secondary care.

- Individuals within the model can only be assigned to one bowel pathology category at the time of the index test (CRC, AAs, LRAs, IBD or NSBP). Patients who have co-existing conditions (e.g., CRC and AAs) are assigned to the most advanced bowel pathology group at the time of the index test.
- Only potentially clinically significant polyps are included, based on the number of people referred for further luminal investigations following a CCE in the NHSE CCE Pilot Study[40] (see Section 4.3.3.1).
- Patients with relevant bowel pathology who are missed by the testing strategy may experience further progression of that pathology during the period of diagnostic delay. This is accounted for in the estimates of lifetime outcomes and costs in the long-term model (see Section 4.3.2.3).
- The only CCE product considered in the economic model is PillCam COLON 2 (Medtronic Ltd.). CCE is assumed to detect only significant bowel pathology (CRC, polyps or IBD). Whilst other video capsule endoscopy products are available for the detection of other GI pathologies, these are not considered in the model.
- The diagnostic accuracy of the diagnostic tests is assumed to be independent of cancer stage or severity of IBD.
- The diagnostic accuracy of the tests is assumed to differ according to underlying pathology (CRC, LRAs, AAs, IBD) but is assumed to be the same across each of the three main populations (symptomatic FIT <10μg/g, symptomatic FIT 10-100μg/g and post-polypectomy surveillance groups).
- All patients who enter the model are fit enough to undergo COL and to receive subsequent active or palliative treatment for any underlying pathology detected.
- The model includes separate analyses for people who are willing and able to undergo COL (denoted "COL-eligible") and people who initially decline COL (denoted "COL-ineligible"). The model assumes that for people who initially decline COL, the only options for the index and replacement tests are CCE or CTC. Based on advice from the EAG's clinical advisors, most of these patients will later undergo COL/FSIG if significant bowel pathology is detected and subsequent biopsy or polypectomy are required.
- Because COL involves the direct visualisation of the bowel and because polypectomy can usually be performed as part of the procedure without the need for additional diagnostic tests, it is assumed to have perfect specificity. Therefore, the model assumes that COL does not result in FP diagnoses which would trigger referral for additional tests. This assumption has also been made in several other economic models.[116, 125, 128] CTC and CCE are assumed to have imperfect specificity and can result in FP diagnoses which lead to referral for further subsequent tests in people with NSBP. The diagnostic accuracy of FSIG is assumed to be equivalent to that for diagnostic COL (within the distal colon).

- Completion rates for CCE, COL and CTC are assumed to differ. The same completion rates for each test are applied across the three main populations.
- Incomplete tests are assumed to require further investigation. For COL, if a patient is unable to complete the index test due to inadequate bowel preparation, they are assumed to be re-offered COL at a later appointment. Some patients with an incomplete COL despite adequate bowel preparation may also be re-offered COL. For index CCE or CTC tests, an alternative test will be used regardless of the reason for incompletion (COL or FSIG if eligible, or alternative tests if COL-ineligible). Regardless of the reason for the incomplete index test, the replacement test is associated with the additional costs of a subsequent appointment and re-testing, but is not assumed to lead to negative impacts on time to diagnosis or the development of more advanced disease.
- If the index diagnostic test is incomplete, the full costs of the failed test are included.
- The model assumes that incomplete CCE and CTC may be partially diagnostic, allowing a proportion of subsequent tests (either replacement or confirmatory) to be limited to examination of the distal colon using FSIG rather than examination of the whole colon using COL.
- In instances in which the index test is incomplete, the model assumes that this test may still result in complications. Replacement tests are assumed to be complete in all cases, and these tests provide diagnostic information and are associated with further risks of complications.
- For people who have an incomplete index COL, FSIG is assumed only to be used to confirm or treat pathology identified by a previously completed test.
- Each confirmatory COL/FSIG is assumed to detect all pathology previously identified by the index/replacement test. Uptake of confirmatory tests is assumed to be 100%.
- For patients with LRAs, if the index test was COL or the replacement test was COL or FSIG, the endoscopist would remove the polyps at the same visit and therefore, an additional therapeutic COL/FSIG procedure would not be required.
- For patients with AAs undergoing COL/FSIG, the model assumes that 90% of these can be removed by polypectomy during the index/replacement test, whilst the remaining 10% are “complex polyps” which require a subsequent COL/FSIG procedure.
- Patients with polyps identified at CCE or CTC would be referred for COL/FSIG.
- All tests (index, replacement and confirmatory) are associated with a risk of complications. These include: bleeding, perforation, and death for COL; perforation and an increased risk of developing CRC due to ionising radiation exposure for CTC, and aspiration and retention for CCE. All complications are assumed to lead to additional costs. Perforation, bleeding, exposure to ionising radiation and capsule retention are each assumed to lead to QALY losses. Capsule aspiration does not incur QALY losses as this complication is assumed to be resolved quickly with no lasting deleterious effects. As noted in Section 4.3.2.2, the model applies the risks of

complications from all tests (the index test, the replacement test and the confirmatory test), with the exception that retention is assumed only to occur in cases of incomplete index CCE tests.

- The model assumes that capsule retention can result only from an incomplete CCE test. As replacement tests and confirmatory tests are always assumed to be complete, the model applies the risk of retention only to incomplete index CCE tests. The model assumes that 50% of patients with an incomplete CCE do not report excretion of the capsule[66] and subsequently undergo an abdominal X-ray to exclude the possibility of retention, with a further CT scan required to provide information on capsule location in patients with confirmed retention.
- Owing to the short time horizon of the decision tree, the risk of death in people who do not experience a fatal test-related complication is assumed to be zero.
- People with NSBP and those with timely diagnosed LRAs and AAs which do not progress to CRC are assumed to have survival and QALY gains equivalent to the age- and sex-matched general population. For people with LRAs and AAs, the model assumes that following polypectomy, the risk of developing CRC returns the average risk for the general population.
- People with IBD are assumed to incur the costs of IBD treatment and lower HRQoL, depending on disease severity and complications.
- People with relevant bowel pathology who are missed by the index/replacement test are assumed to incur a risk of CRC stage shift, progression of adenomas or worsening severity of IBD, thereby leading to reductions in lifetime QALYs and altering lifetime treatment costs.
- All tests (index, replacement or confirmatory) are associated with the costs of bowel preparation, where necessary, and a pre-assessment/consultation phone call with a nurse.
- All completed tests are assumed to require follow-up communicate the test results. The model includes the cost of a consultant-led face-to-face appointment for patients with a confirmed diagnosis of CRC and the cost of a letter explaining the test results for all patients with any underlying diagnosis other than CRC.

4.3.3. Evidence used to inform the model parameters

Table 31 summarises the evidence used to inform the model parameters. A detailed description of these evidence sources is provided in the subsequent sections. Data from the NHSE CCE Pilot Study[40] are used to inform key model parameters relating to prevalence, the CCE completion rate and the use of FSIG/COL as a subsequent luminal investigation. Where available, estimates for other key model parameters have been drawn from previous systematic reviews and meta-analyses which have been identified from targeted searches in MEDLINE undertaken by the EAG. Where multiple studies were identified, studies were preferred if they were undertaken in a UK setting, and/or if they were consistent with estimates used in the previous NICE appraisal of FIT to guide CRC pathway referral in primary care (DG56).[127] Unit costs were based on estimates provided by the company, literature and routine costing sources.

Table 31: Summary of evidence used to inform the model parameters

Parameter group	Source
Short-term model	
Prevalence of CRC, AAs, IBD and no pathology	NHSE CCE Pilot Study[40] and EAG's meta-analysis (see Section 3.3.2.2)
Diagnostic test accuracy – CCE	EAG's meta-analysis (see Section 3.3.2.2)
Diagnostic test accuracy – COL	Burr *et al.*,[129] Martin-Lopez *et al.*,[130] Pera *et al.*[131] and Horsthuis *et al.*[132]
Diagnostic test accuracy – CTC	
Completion rate – CCE	NHSE CCE Pilot Study[40]
Completion rate – COL	Plumb *et al.*[133]
Completion rate – CTC	Deding *et al.*[134]
Proportion of CCEs which are incomplete due to inadequate bowel preparation or other reasons	NHSE CCE Pilot Study[40]
Proportion of COLs which are incomplete due to inadequate bowel preparation or other reasons	Britton *et al.*[135]
Proportion of CTCs which are incomplete due to inadequate bowel preparation or other reasons	Liedenbaum *et al.*[136]
Probability of CCE complications (aspiration, retention)	Thorndal *et al.*[137] and Wang *et al.*[138]
Probability of COL complications (bleeding, perforation and death)	Reumkens *et al.*[139]
Probability of CTC complications (perforation and CRC risk due to exposure to ionising radiation)	Bellini *et al.*[140] and Brenner *et al.*[141]
QALY losses due to test complications	QALY losses due to bleeding and perforation from Thomas *et al.*,[125] Dorian *et al.*[142] and Ara and Brazier *et al.*[143] HRQoL impact of CCE aspiration assumed to be zero. QALY losses due to CCE retention based on Malcolm *et al.*[144] QALY losses due to ionising radiation-related CRC based on difference between general population QALYs versus QALYs for people with CRC, estimated using MiMIC-Bowel.[125]
Procedure/visit costs of COL/FSIG (with/without polypectomy), CCE and CTC, X-ray and CT	NHS Reference Costs 2022/23[117]
Cost of managing complications	NHS Reference Costs 2022/23[117] and Thomas *et al.*[125]
Cost of CCE capsule	Manufacturer (Medtronic Ltd.)
Proportion of further luminal investigations using FSIG vs COL	NHSE CCE Pilot Study[40]
Long-term models	
Long-term LYGs, QALYs and costs in people with CRC and AAs (with or without diagnostic delay), symptomatic population	Re-analysis of the MiMiC-Bowel model (Thomas *et al.*[125]) and analysis of additional diagnostic delays reported by Whyte *et al.*[122] (see Appendix 7).
Long-term LYGs, QALYs and costs in people with CRC and AAs (with or without diagnostic delay), surveillance population	
Long-term LYGs, QALYs and costs in people with IBD	Survival based on ONS life tables for England.[123] Utility values and costs informed by DG56 model.[127]
Long-term LYGs, QALYs and costs in people with NSBP	Survival based on ONS life tables for England.[123] Utility values based on Hernandez Alava *et al.*[126]

CRC - colorectal cancer; AA - advanced adenoma; IBD - inflammatory bowel disease; NHSE - National Health Service England; CCE - colon capsule endoscopy; CTC - computed tomography colonography; HRQoL - health-related quality of life; QALY - quality-adjusted life year; LYG - life year gained; ONS - Office for National Statistics; EQ-5D-3L - Euroqol 5-Dimensions 3-Level; NSBP - no significant bowel pathology; DG - Diagnostics Guidance

4.3.3.1. Prevalence of underlying pathology (CRC, AAs or IBD)

The prevalence of significant underlying bowel pathology in each analysis population was informed by data from the NHSE CCE Pilot Study,[40] the EAG's meta-analysis of the diagnostic test accuracy of CCE (see Section 3.3.2.2) and other external data.[131] The NHSE CCE Pilot Study Investigators provided aggregate data on the number of people in the study who were detected by CCE as having CRC, polyps sized ≥10mm, polyps sized <10mm, IBD or NSBP within each of the three main analysis populations included in the model (see Table 32). These data relate to CCE-detected yield and therefore the reported number of people with polyps, CRC or IBD in the dataset may include FPs and exclude FNs, whilst the reported number of people with NSBP may include FNs and exclude FPs. The NHSE CCE Pilot Study Investigators also provided separate aggregate data on the final diagnosis amongst the subset of patients in the pilot who were referred for further luminal investigation using COL/FSIG following the initial CCE (see Table 33). The latter dataset was only available for the overall symptomatic population (data were not split by FIT 10-100µg/g and FIT <10µg/g subgroups) and for those surveillance patients who were referred for immediate further tests (patients with deferred further investigations were not included). The dataset includes the number of referred people with polyps, but these are not split by size (≥10mm or <10mm). This latter dataset therefore reflects those patients with polyps and other CCE-detected pathology warranting referral for further investigation and adjusts for FPs arising from the initial CCE, but does not include FNs who were not referred for further luminal investigation after the index CCE.

Table 32: CCE yield data from the NHSE CCE Pilot Study, split by analysis population

CCE-indicated pathology	Symptomatic FIT 10-100µg/g		Symptomatic FIT <10µg/g		Surveillance	
	Number	Proportion	Number	Proportion	Number	Proportion
CRC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥10mm polyps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<10mm polyps	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IBD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CCE - colon capsule endoscopy; FIT - faecal immunochemical test; CRC - colorectal cancer; IBD - inflammatory bowel disease; NSBP - no significant bowel pathology

Table 33: Estimated prevalence of underlying pathology amongst patients who had a subsequent COL/FSIG following CCE in the NHSE CCE Pilot Study

COL/FSIG confirmed pathology	Symptomatic (FIT 10-100µg/g and <10µg/g		Surveillance	
	Number	Proportion	Number	Proportion
CRC	[redacted]	[redacted]	[redacted]	[redacted]
Polyps	[redacted]	[redacted]	[redacted]	[redacted]
IBD	[redacted]	[redacted]	[redacted]	[redacted]
NSBP*	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

COL - colonoscopy; FSIG - flexible sigmoidoscopy; FIT - faecal immunochemical test; CRC - colorectal cancer; IBD - inflammatory bowel disease; NSBP - no significant bowel pathology
** Missing data in the NHSE dataset are assumed to be in the NSBP group.*

Neither the data on CCE yield nor the data on patients referred for COL/FSIG after CCE are likely to fully reflect the true underlying prevalence of each pathology group within the analysis populations relevant to the decision problem. As such, the EAG applied several adjustments to the data for referred patients in order to: (a) account for FNs who will be missing from the dataset, (b) include deferred patients who are not included in the surveillance population, (c) split the prevalence for symptomatic patients by FIT score (10-100µg/g vs <10µg/g) and (d) split the aggregated polyp data according to size (≥10mm vs <10mm). The following adjustments were applied:

- *CRC.* [redacted] The EAG's model assumes that all of these CRCs occurred in the FIT 10-100µg/g population. This assumption is broadly in line with the findings of a Danish study which evaluated FIT in patients without alarm symptoms and found that the risk of CRC was <0.1% in those with a FIT of <10µg/g.[145] Prevalence was estimated by dividing the number of CRCs in referred patients (Table 33) by the EAG's meta-analysis estimate of the sensitivity of CCE for ≥10mm polyps (sensitivity = 0.85) to account for potential FNs missing from the referred population.
- *Polyps in symptomatic patients.* The prevalence of polyps in all symptomatic patients was estimated by dividing the number of people with polyps in the referred population by the EAG's meta-analysis estimate of the sensitivity of CCE for ≥10mm polyps (sensitivity = 0.85) to account for potential FNs. The proportion of people with polyps in each FIT population was based on the proportion of people with polyps in the CCE yield data ([redacted]). The proportion of people with polyps in each size category (≥10mm vs <10mm) in each FIT population was then estimated based on the proportion of all people with ≥10mm or <10mm polyps in the CCE yield data.
- *Polyps in surveillance patients.* The prevalence of polyps in all surveillance patients was estimated by assuming that all deferred patients have polyps, adding these to the number of referred patients with polyps, and then dividing the total number of people with polyps by the EAG's meta-analysis estimate of the sensitivity of CCE for ≥10mm polyps (sensitivity = 0.85) to account for potential missing FNs.
- *IBD.* The prevalence of IBD was estimated by dividing the number of IBD cases in referred patients by the assumed sensitivity of CCE for detecting IBD from the literature[131] (sensitivity = 0.89, see Section 4.3.3.2). The proportion of IBD cases occurring in each of the FIT 10-100µg/g and <10µg/g populations was estimated based on the proportions of cases seen in each FIT population in the CCE yield data.
- *NSBP.* In each analysis population, the number of people with NSBP was calculated as the total number of patients undergoing CCE minus the total number of patients with significant bowel pathology (polyps, CRC or IBD) based on the adjustments described above.

Based on these adjustments, the estimated underlying prevalence of each pathology type within each analysis population is shown in Table 34. These estimates are applied in the EAG's model.

Table 34: Estimated true underlying prevalence applied in the EAG's model

CCE-indicated pathology	Symptomatic FIT 10-100µg/g		Symptomatic FIT <10µg/g		Surveillance	
	Number	Proportion	Number	Proportion	Number	Proportion
CRC	[redacted]					
≥10mm polyps						
<10mm polyps						
IBD						
NSBP						
Total						

FIT - faecal immunochemical test; CRC - colorectal cancer; IBD - inflammatory bowel disease; NSBP - no significant bowel pathology

4.3.3.2. Diagnostic test accuracy for CCE, COL and CTC

The estimates of the diagnostic accuracy of CCE, COL and CTC applied in the base case analysis are summarised in Table 35. Estimates of diagnostic test accuracy for CCE were based on the EAG's meta-analysis and assumptions (see Section 3.3.2.2). The diagnostic accuracy of COL and CTC was based on published systematic reviews and population-based studies.[129, 130, 132]

Table 35: Sensitivity and specificity estimates applied in the economic model

Pathology	Parameter	Test*	Point estimate	95% CI	Source
CRC	Sensitivity	CCE	0.851	0.703 to 0.939	Assumed to be the same as sensitivity of CCE for ≥10mm polyps
		COL	0.935	0.931 to 0.939	Burr *et al.*[129]
		CTC	0.912	0.865 to 0.946	Assumed to be the same as sensitivity of CTC for lesions >10mm
AAs	Sensitivity	CCE	0.851	0.703 to 0.939	EAG meta-analysis (≥10mm polyps)
		COL	0.929	0.860 to 0.971	Martin-Lopez *et al.*[130]
		CTC	0.912	0.865 to 0.946	Martin-Lopez *et al.*[130]
LRAs	Sensitivity	CCE	0.830	0.703 to 0.914	EAG meta-analysis (≥6mm polyps)
		COL	0.867	0.813 to 0.910	Martin-Lopez *et al.*[130]
		CTC	0.771	0.733 to 0.805	Martin-Lopez *et al.*[130]
IBD	Sensitivity	CCE	0.892	0.861 to 0.919	Assumed to be the same as COL
		COL	0.892	0.861 to 0.919	Pera *et al.*[131]
		CTC	0.843	0.75 to 0.918	Horsthuis *et al.*[132]
NSBP	Specificity	CCE	0.904	0.817 to 0.974	EAG meta-analysis (≥10mm polyps)
		COL	Assumed to be 1.0 due to nature of test		
		CTC	0.803	0.777 to 0.828	Based on global specificity for CTC reported by Martin-Lopez *et al.*[130]

CRC - colorectal cancer; AA - advanced adenoma; LRA - low-risk adenoma; IBD - inflammatory bowel disease; CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; CI - confidence interval; EAG - External Assessment Group; NSBP - no significant bowel pathology

** Where FSIG is used as a replacement test, it is assumed to have equivalent diagnostic accuracy to COL*

The sensitivity and specificity of CCE for detecting CRC and polyps was taken from the EAG's meta-analysis (see Section 3.3.2.2). The sensitivity of CCE for detecting LRAs and AAs was based on the estimates obtained from the meta-analyses for ≥6mm polyps and ≥10mm polyps, respectively. As insufficient data were available to provide a reliable estimate of the sensitivity of CCE for detecting CRC, this was assumed to be equivalent to the sensitivity of CCE for detecting ≥10mm polyps. Insufficient evidence was available to estimate the sensitivity of CCE in detecting IBD; hence, CCE was assumed to be equivalent to COL, which in turn was informed by Pera *et al.*[131] The specificity of CCE was based on the meta-analysis for ≥10mm polyps.

The sensitivity of COL for detecting CRC was taken from a population-based study of post-colonoscopy colorectal cancer (PCCRC) rates in the NHS in England reported by Burr *et al.*[129] Within this study, the authors generated a dataset of people who had undergone a COL in the English NHS between January 2005 and December 2013. Data were linked from inpatient and outpatient Hospital Episode Statistics (HES), the English BCSP and the National Cancer Registration and Analysis Service (NCRAS) datasets. PCCRCs were defined as detected CRCs which appeared between 6 and 36 months after a preceding COL (defined as FNs within the study design). The authors report an overall unadjusted PCCRC rate of 7.4% over the study period, with a higher rate of 9.0% in 2005 and a lower rate of 6.5% in 2013. The EAG's economic model applies the most recent estimate available (PCCRC rate = 6.5%) and therefore assumes a sensitivity of COL for CRC of 93.5%.

Estimates of the sensitivity of COL and CTC for detecting colorectal polyps were taken from a systematic review reported by Martin-Lopez *et al.*[130] This review included nine studies which recruited asymptomatic individuals or those with non-specific symptoms of CRC (e.g., chronic constipation or chronic abdominal pain) which were published up to 2009, covering an analysis population of 5,640 patients. Studies were included if patients underwent CTC and COL and if the reference standard was histological diagnosis and/or COL for verification. Pooled estimates of the sensitivity and specificity of CTC and COL are reported according to polyp size (5-7mm; 8-10mm and >10mm). Within the economic model, the sensitivity of CTC and COL for LRAs was assumed to reflect the 5-7mm polyp group, whereas the sensitivity of CTC and COL for AAs was assumed to reflect the >10mm group. Estimates are based on the diagnostic accuracy of the tests per person rather than per lesion. No estimate of the sensitivity of CTC for detecting CRC was reported by Martin-Lopez *et al.*; instead, this was assumed to be equivalent to the sensitivity of CTC for detecting >10mm polyps.

The sensitivity of COL for detecting IBD was taken from a diagnostic accuracy study of 442 endoscopies in 254 patients with CD or UC reported by Pera *et al.*[131] Estimates of the sensitivity of CTC in detecting IBD were taken from a systematic review reported by Horsthuis *et al.*[132] This review included studies of the diagnostic accuracy of ultrasound (US), magnetic resonance imaging (MRI),

CT, scintigraphy and positron emission tomography (PET) in the diagnosis of IBD published during the period 1993 to 2006. The review included 33 studies undertaken in individuals with a history or symptoms of IBD. Pooled sensitivity and specificity estimates were calculated using a bivariate model. Mean sensitivity and specificity estimates for CT were reported to be 84.3% and 95.1%, respectively (95% CI not reported). These estimates for CT were assumed to be applicable to CTC as no other evidence could be identified by the EAG.

Within the economic model, COL is assumed to have perfect specificity because it involves direct visualisation of the bowel and an FP identified at COL would generally not require a further diagnostic test; this assumption is in line with previous economic models of screening interventions.[116, 125, 128, 146] Conversely, CCE and CTC are assumed to be have imperfect specificity, meaning that these tests may lead to FP test results in a proportion of patients.

These estimates of diagnostic accuracy are used in all three main analysis populations (symptomatic FIT <10µg/g, symptomatic FIT 10-100µg/g and post-polypectomy surveillance groups), thereby assuming that the diagnostic performance of each test would be the same in symptomatic and surveillance patients.

Overall, the EAG's model assumes that for CRC and AAs, CCE is less sensitive than both COL and CTC. For LRAs, CCE is assumed to be more sensitive than CTC but less sensitive than COL. COL is assumed to have perfect specificity (because an FP result would not trigger referral for further tests) whereas CCE and CTC are assumed to result in a non-negligible proportion of FP diagnoses in people with NSBP. The EAG notes that there is considerable uncertainty around the comparative accuracy of CCE, COL and CTC, and several other published meta-analyses of the diagnostic accuracy of CTC and COL are available from the literature (see Appendix 8). Alternative estimates of the sensitivity and specificity of all tests, including scenarios in which the accuracy of CCE is assumed to be equivalent to CTC and COL, are explored in sensitivity analyses (see Section 4.3.6.4).

4.3.3.4. Completion rates for CCE, COL and CTC

A summary of the test completion rates for CCE, COL and CTC applied in the EAG's model is presented in Table 36.

Table 36: Completion rates for CCE, COL and CTC applied in the economic model

Test	Mean	95% CI	Source
CCE	[redacted]	[redacted]	NHSE CCE Pilot Study[40]
COL	0.92	0.91 to 0.92	Plumb *et al.*[133]
CTC	0.98	0.96 to 1.00	Deding *et al.*[134]

CI - confidence interval; CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; EAG - External Assessment Group; NHSE - National Health Service England

The completion rate for CCE was based on data from the NHSE CCE Pilot Study.[40] Within this study, a total of [redacted] CCEs were administered to patients across all three populations and [redacted] of these were complete.

The completion rate for COL was estimated from data reported from a retrospective analysis of a patient experience questionnaire applied to patients undergoing follow-up tests as part of the English BCSP (Plumb *et al.*[133]). The study reports on the experience of patients undergoing a colonic test (COL or CTC) following a positive FOBT based on a standard questionnaire sent to individuals 30 days after the process. The study included screenees tested between January 2011 and December 2012, thereby covering the first two calendar years after the roll-out of the screening programme. Amongst 67,114 potentially eligible screenees who underwent a colonic investigation, 52,805 individuals returned a questionnaire, of which 52,202 questionnaires were analysed (50,975 for COL and 1,970 for CTC). The paper includes a flowchart which details the number of patients who had a COL alone, a COL followed by another test, or another test followed by a COL. The flowchart indicates that 50,804 individuals underwent COL as their initial follow-up test, and 4,231 of these went on to receive an alternative test. The precise reasons for patients undergoing an alternative test after COL are not described in the paper; the EAG assumes that the primary reason was because the COL was incomplete. This indicates a completion rate for COL of 91.67% (95% CI 0.91 to 0.92).

The completion rate for CTC was based on a systematic review of completion rates and the diagnostic accuracy of CCE versus CTC following incomplete COL reported by Deding *et al.*[134] The review included studies published prior to September 2020 and included RCTs, paired studies, cohort and case-control studies. A total of 26 studies were included in the analysis. All CCE studies were undertaken in European populations, whereas the CTC studies included European, Asian and American populations. The authors report a pooled estimate of the completion rate for CTC of 0.98 (95% CI 0.96 to 1.00).

The EAG notes that the probability that a patient has an incomplete index test followed by an incomplete replacement test is expected to be very low. In order to avoid an intractably complicated model structure, the EAG's model assumes that only the index test can be incomplete; replacement and confirmatory tests are assumed to have a completion rate of 100%.

4.3.3.5. Proportion of incomplete tests due to inadequate bowel preparation or other causes

The proportion of CCEs which are incomplete due to inadequate bowel preparation was obtained from the NHSE CCE Pilot Study.[40] Amongst the [redacted] CCEs which were incomplete, [redacted] were due to inadequate bowel preparation and the remaining [redacted] CCEs were due to reasons other than inadequate bowel preparation. The EAG's model assumes that all patients with an incomplete CCE would receive an alternative diagnostic test, regardless for the reason for the test being incomplete (COL or FSIG where possible).

The proportion of COLs which are incomplete due to inadequate bowel preparation was based on a 5-year audit of COLs performed between April 2005 and 2010 at the Royal Liverpool University Hospital reported by Britton *et al.*[135] Within this study, the authors report that 693 of 10,580 COLs were incomplete and that 24.8% of the incomplete COLs were due to inadequate bowel preparation. Amongst patients who went on to have a further investigation, 35.8% of patients underwent a repeat COL. This latter value is used in the model.

The proportion of incomplete CTCs due to inadequate bowel preparation was taken from an analysis of data collected from an FOBT pilot screening trial in the Netherlands reported by Liedenbaum *et al*.[136] Amongst ten patients who had an incomplete CTC, four cases (40%) were incomplete due to insufficient bowel preparation. The remaining six cases (60%) were due to insufficient bowel distension.

As noted in Section 4.3.2.2 the economic model assumes that all patients with an incomplete CCE or CTC would be offered a different test regardless of the reason for the test being incomplete (COL or FSIG where possible).

4.3.3.6. Probability of complications for CCE, COL and CTC

A summary of the risks of complications for each test applied in the EAG's model is presented in Table 37. The economic model includes risks of complications for all tests. Perforation is included as a possible complication of both COL and CTC. Increased lifetime CRC risk due to exposure to ionising radiation is included as a complication for CTC only. Bleeding is included as a complication for COL only. Capsule retention and aspiration are included as complications of CCE. Where available, the risks of these complications were taken from published systematic reviews.[137-140]

Table 37: Risks of complications applied in economic model

Complication*	Probability (95% CI)	Source
Perforation due to COL, with polypectomy	0.0008 (0.0006 to 0.0010)	Reumkens *et al.*[139]
Perforation due to COL, without polypectomy	0.0004 (0.0002 to 0.0008)	
Post-COL bleeding, with polypectomy	0.0098 (0.0077 to 0.0121)	
Post-COL bleeding, without polypectomy	0.0006 (0.0002 to 0.0011)	
Post-COL mortality, with/without polypectomy	0.00003 (0.00001 to 0.00006)	
CTC perforation	0.0004 (0.0000 to 0.0010)	Bellini *et al.*[140]
CTC lifetime risk of colon cancer (weighted)	[redacted] (95% CI not reported)	Brenner *et al.*[141] Male:female weighting informed by NHSE CCE Pilot Study[40]
CCE retention	0.0064 (0.0040 to 0.0093)	Wang *et al.*[138]
CCE aspiration	0.001 (0.001 to 0.002)	Thorndal *et al.*[137]

*CI - confidence interval; COL - colonoscopy; CTC - computed tomography colonography; NHSE - National Health Service England; CCE - colon capsule endoscopy *Risks of complications for FSIG assumed to be the same as those for COL.*

The risks of perforation, bleeding and mortality associated with COL were based on a systematic review reported by Reumkens *et al.*[139] This review included population-based studies of post-COL complications in patients undergoing COL between January 2001 and December 2015. The review defined post-COL complications as perforations, post-COL bleeding or mortality events occurring within 30 days of the COL procedure, regardless of the COL indication. Perforation was defined as the presence of X-ray abnormalities requiring hospitalisation or surgery. Post-COL bleeding was defined as bleeding after COL, with or without polypectomy which required hospitalisation, an emergency room (ER) visit, the need for a repeat COL, or transfusion of packed red blood cells. Bleeding events which were treated and stopped during the index COL were not included as events in the analysis. Mortality was defined as deaths which occurred within the 3 months following a COL procedure due to cardiorespiratory events, perforation or bleeding related to the procedure. The review included 21 studies, covering a total of 1,996,340 COL procedures. The included studies were undertaken in Europe (N=10), North America (N=7), South Korea (N=3) and New Zealand (N=1). Studies included screening/surveillance and symptomatic populations. The study reports an overall perforation rate of 0.5/1,000 COLs (95% CI 0.4 to 0.7), an overall post-COL bleeding rate of 2.6/1,000 COLs (95% CI 1.7 to 3.7) and an overall mortality rate of 2.9/100,000 COLs (95% CI 1.1 to 5.5). The risks of perforation and bleeding were higher in patients with polypectomy compared to those without polypectomy.

The risks of perforation associated with CTC were based on a systematic review and meta-analysis reported by Bellini *et al.*[140] This review was undertaken to assess the perforation rate associated with CTC, and to identify potential clinical or technical predictors of perforation. The review included 11

studies which were reported up to August 2013, covering a total of 103,399 patients. The included studies were undertaken in the UK (N=3), the US (N=3), the Netherlands (N=1), Italy (N=1), Israel (N=1), Australia (N=1), and one study was undertaken in multiple countries. Study populations included screening and symptomatic patients. The authors report an overall risk of perforation due to CTC of 0.04% (95% CI 0.00% to 0.10%). No CTC-related deaths were reported in any of the included studies; hence, death resulting from perforation following CTC is not included in the EAG's model.

The absolute lifetime colon cancer risk associated with ionising radiation exposure from CTC was taken from a report by Brenner *et al.*[141] This study estimated the excess cancer risk associated with the radiation exposure from a paired CTC scan for a healthy 50-year-old. The sex-specific additional absolute lifetime risks of different cancers were reported, and the lifetime colon cancer risk was reported to be 0.044% for men and 0.038% for women (95% CIs not reported). The EAG's economic model applies a weighted risk of [redacted] assuming that [redacted] of the target population for CCE is female (based on the NHSE CCE Pilot Study[40]). This complication is applied as a QALY loss to all patients who complete the CTC procedure, except for those who already have underlying CRC at the point of testing.

The risk of capsule retention was based on a systematic review and meta-analysis of AEs of video capsule endoscopy reported by Wang *et al.*[138] The review identified 402 studies, including 108,079 procedures which included but were not limited to CCE. Separate data are presented by capsule type. Based on 26 studies of CCE, there were 22 reported cases of capsule retention out of 3,432 procedures. The economic model applies a retention rate for CCEs of 0.0064 (95% CI 0.0040 to 0.0093). [redacted]. Within the model, the retention risk is applied only to patients with an incomplete index CCE (conditional risk calculated as 0.0064/[redacted]) whereas the risk of retention in patients with a complete CCE is assumed to be zero (expected value = [redacted] = 0.0064).

The risk of capsule aspiration was taken from a systematic review of aspiration rates in people undergoing capsule endoscopy reported by Thorndal *et al.*[137] The review included studies published between 1996 and 2022 and included observational cohort studies, case reports and case series. The review included a total of 57 studies of people undergoing capsule endoscopy, which included but were not limited to CCE. Amongst these, 12 were observational studies and the remaining 45 studies were case series or case reports. The countries in which the studies were undertaken are not reported in the paper. Based on the 12 observational studies, a total of 16 capsule aspiration events were reported across approximately 14,522 examinations, leading to an estimated aspiration rate of 0.001 (95% CI 0.001 to 0.002). [redacted]

4.3.3.7. QALY losses resulting from diagnostic test complications

Estimates of QALY losses associated with complications of CCE, COL and CTC applied in the economic model are summarised in Table 38.

Table 38: QALY losses associated with test complications included in the EAG model

Complication	Test(s)	QALY loss (per event)	Source
Perforation	COL and CTC	0.0025	MiMiC-Bowel,[125] based on estimates from Ara & Brazier[143]
Bleeding	COL	0.0014	MiMiC-Bowel,[125] based on estimates from Dorian *et al.*[142]
Death	COL and CTC	N/a*	-
CRC due to ionising radiation exposure	CTC	4.19	Based on estimated mean QALYs lost amongst those with CRC vs general population in MiMiC-Bowel[125]
Capsule retention	CCE	0.0092	Based on estimated QALYs lost by those undergoing surgical removal of capsule versus general population QALYs[138, 144]
Capsule aspiration	CCE	0.00	Assumption

QALY - quality-adjusted life year; COL - colonoscopy; CTC - computed tomography colonography; CCE - colon capsule endoscopy

**QALY losses resulting from COL-related death are captured elsewhere in model through calculation of the decision tree expected values. The CTC mortality rate is assumed to be zero based on Bellini et al.[140]*

The QALY losses associated with each perforation and post-COL bleeding event were based on the same assumptions as those applied in the DG56 model,[127] which in turn, are consistent with estimates used in the MiMiC-Bowel model.[125] The utility value for a serious bleeding event was taken from Dorian *et al.*[142] and was assumed to last for 2 weeks. QALY losses resulting from non-fatal perforations were based on Ara and Brazier,[143] with the disutility value based on the absolute difference in mean Euroqol 5-Dimenions 3-Level (EQ-5D-3L) score in patients with and without 'stomach ulcer/abdominal hernia/rupture'; this event was assumed to impact on HRQoL for a duration of 1 month.

QALY losses associated with an increased cancer risk resulting from exposure to ionising radiation during the CTC procedure were informed by Brenner *et al.*[141] The sex-specific lifetime colon cancer risks reported by Brenner *et al.* were weighted based on the proportionate split of men and women in the EAG's model, and the weighted colon cancer risk was incorporated into the long-term model payoffs in terms of QALY losses for patients who had a complete CTC test either as the index or replacement test. The model assumes that there is no excess lifetime risk of radiation-associated colon cancer in patients who have already been diagnosed with CRC in the decision tree. The detailed calculation of QALY losses is as follows.

The lifetime QALY loss associated with CRC was assumed to be similar in both the symptomatic and surveillance populations, and was estimated using the results of the analyses reported by Whyte *et al.*[122] Firstly, the lifetime QALYs for patients with CRC who are diagnosed without additional delays were

weighted based on the CRC stage distribution at diagnosis under the 2WW system.[124] Then, the EAG calculated the health decrements/additional QALY losses due to CRC relative to the lifetime QALYs estimated for the NSBP group (see Table 39). This suggests a loss of 4.19 QALYs per person diagnosed with CRC. This QALY loss was then multiplied by the excess risk of developing CRC due to ionising radiation exposure from Brenner *et al.*[141] (4.19 x [redacted] = [redacted] QALYs lost per person undergoing CTC).

Table 39: Lifetime QALY losses from having CRC (without additional diagnostic delay)

Description	Mean value
Lifetime QALYs gained (CRC with no diagnostic delay)*	7.31
Lifetime QALYs gained (NSBP)	11.50
Lifetime QALY loss due to CRC	4.19
Expected QALY loss due to CRC resulting from exposure to ionising radiation†	[redacted]

CRC - colorectal cancer; QALY - quality-adjusted life year; NSBP - no significant bowel pathology
**Weighted lifetime QALYs gained based on the cancer stage distribution at diagnosis*
†Sex-weighted lifetime colon cancer risk applied.

QALY losses associated with capsule retention were assumed to be dependent on the type of subsequent treatment or procedure used for capsule retrieval. Wang *et al.*[138] reported that amongst capsule retention cases, 45.95% of patients had surgery, 25.98% underwent endoscopy, 5.10% received medical treatment and 22.98% received no intervention. The model assumes that only the surgical removal of a retained capsule would lead to lasting adverse impacts on patient HRQoL. The utility value associated with post-surgical recovery was based on a study of long-term HRQoL following CRC surgery reported by Malcolm *et al.*[144] This study reports a mean EQ-5D value of 0.795. The disutility associated with surgery was estimated by subtracting this utility value from the weighted EQ-5D-3L value for the general population at model entry. The EAG's model assumes that this disutility persists for 6 months.

Table 40: QALY losses for capsule retention

Description	Mean value
Utility value following colorectal surgery	0.795
Age- and sex-weighted utility value for general population at model entry (age = [redacted], female = [redacted])	0.835
Disutility associated with surgery	0.040
QALY loss due to surgical procedure to remove capsule	0.02
Proportion of retention cases which require surgical removal	45.95%
Expected QALY loss per capsule retention	0.0092

QALY - quality-adjusted life year; EQ-5D - Euroqol 5-Dimensions; CRC - colorectal cancer

Capsule aspiration was assumed to be resolved quickly without any lasting detrimental impact on patient HRQoL. Therefore, no QALY loss is included in the model for this complication.

4.3.3.8. Costs associated with diagnostic tests

The costs of diagnostic tests per procedure included in the EAG's economic model are summarised in Table 41. The model includes the costs associated with preparing for and administering the test as well as the costs of subsequent appointments or a letter to communicate the test results to the patient. The costs of bowel preparation and booster medications applied in the model can be found in Appendix 9 (Table 68 and Table 69).

Table 41: Costs of diagnostic tests applied in the EAG's model

Diagnostic test (completed)	Cost of diagnostic test	Cost of bowel preparation	Cost of assessment phone call‡	Cost of follow-up appointment/ letter§	Total cost per completed procedure	Source and assumptions of test costs
CCE*	£735	£51	£24	£195	**£1,005**	PillCam COLON 2 capsule cost provided by the manufacturer (Medtronic Ltd.).
CCE†				£1	**£811**	
Diagnostic COL*	£987	£39	£24	£195	**£1,245**	NHS Reference Costs 2022/23,[117] weighted mean cost of diagnostic colonoscopy with biopsy, 19 years and over (code FE31Z)
Diagnostic COL†				£1	**£1,051**	
Therapeutic COL	£1,023	£39	£24	£1	**£1,087**	NHS Reference Costs 2022/23,[117] weighted mean cost of therapeutic colonoscopy, 19 years and over (code FE30Z)
CTC*	£231	£42	£24	£195	**£492**	NHS Reference Costs 2022/23,[117] weighted mean cost of CTC scans (code RD61Z)
CTC†				£1	**£298**	
FSIG	£856	FSIG costs applied as reduction in procedure cost of £131 relative to diagnostic COL				NHS Reference Costs 2022/23,[117] diagnostic flexible sigmoidoscopy with biopsy, 19 years and over (FE34Z).

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computerised tomography colonography; CT - computed tomography; MRI - magnetic resonance imaging; DG - Diagnostics Guidance

** For patients with underlying CRC*

† For patients with underlying pathology other than CRC

‡ Assumes a 30-minute pre-assessment phone call with a band 5 nurse, estimated from PSSRU, 2023

§ For patients with underlying CRC, the cost of a consultant-led non-admitted face-to-face follow-up consultation visit (WF01A) from NHS Reference Costs 2022/23 was applied. For patients in whom CRC is not diagnosed, the cost of a letter explaining the test results was assumed. A cost of £1.33 is applied based on the cost from MiMiC-Bowel uplifted to 2022/23 prices.

CCE

The cost of a CCE test is estimated to be £735, based on information provided by the manufacturer (Medtronic Ltd.). This net cost includes the costs of the capsule, the sensor belt cover, the maintenance cost per recorder, an outpatient visit at which the capsule is swallowed under supervision and one hour of reading time by a trained endoscopist. The device cost breakdown per procedure is shown in Table 42. In addition, the model includes the following costs associated with preparing for the test and delivering the test result: (i) a first consultation or pre-assessment 30-minute phone call with a Band 5 hospital-based nurse; (ii) bowel preparation and booster medications which include medication costs (see details in Appendix 9, Table 68 and Table 69) and a 30-minute phone call with a nurse, and (iii) follow-up which could be either a face-to-face appointment with a consultant (for CRC-positive cases) or a letter explaining the test results (for diagnoses other than CRC). The total cost of a completed CCE procedure is estimated to be £1,005 for patients with underlying CRC and £811 for patients with a diagnosis other than CRC.

Table 42: Acquisition cost breakdown per CCE procedure

Acquisition cost component	Unit cost	Source
Capsule cost	£460.00	Manufacturer
Sensor belt cover	£5.50	Manufacturer
Annuitised cost of a recorder per patient	£3.07	Assumes 100 patients use each recorder per year. The annuitised cost of each recorder was estimated to be £307.28 based on a 5-year contract cost of £1,125.
CCE reading time	£143.00	PSSRU 2023,[121] cost per hour of a hospital-based medical consultant.
Outpatient costs for swallowing CCE	£123.57	NHS Reference Costs 2022/23,[117] non-admitted face-to-face attendance, first (service code 301, currency code WF01B)
Total acquisition cost per CCE procedure including reading time	£735.14	

DR - data recorder; CCE - colon capsule endoscopy; PSSRU - Personal Social Services Research Unit

Diagnostic colonoscopy

The cost of a diagnostic COL procedure was estimated based on the weighted mean cost of a diagnostic COL with biopsy, 19 years and over, (code FE31Z) from NHS Reference Costs 2022/23.[117] In addition, the model includes the following costs associated with preparing for the test and delivering the test result: (i) a first consultation or pre-assessment 30-minute phone call with a Band 5 hospital-based nurse; (ii) bowel preparation which includes medication costs and a 30-minute phone call with a nurse, and (iii) follow-up which could be either a face-to-face appointment with a consultant (for CRC-positive cases) or a letter explaining the test results (for diagnoses other than CRC).

The total cost of a complete diagnostic COL procedure was estimated to be £1,245 for patients with underlying CRC and £1,051 for patients with a diagnosis other than CRC.

Therapeutic colonoscopy

The cost of a therapeutic COL procedure was based on the weighted mean cost of a therapeutic COL, 19 years and over (code FE30Z) from NHS Reference Costs 2022/23.[117] In addition, the model includes the following costs associated with preparing for the test and delivering the test result: (i) a first consultation or pre-assessment 30-minute phone call with a Band 5 hospital-based nurse; (ii) bowel preparation which includes medication costs and a 30-minute phone call with a nurse, and (iii) a letter explaining the test results. The total cost of a complete therapeutic COL procedure was estimated to be £1,087.

Flexible sigmoidoscopy

The cost of a FSIG procedure was based on the weighted mean cost of a diagnostic flexible sigmoidoscopy with biopsy, 19 years and over (FE34Z) from NHS Reference Costs 2022/23.[117] The cost of FSIG is applied in the model as a reduction in procedure cost relative to diagnostic COL (i.e., £987 minus £856 = £131). This cost reduction is applied to approximately [redacted] of patients undergoing further tests in the symptomatic populations and [redacted] of patients undergoing further tests in the surveillance population, based on the NHSE CCE Pilot Study[40] (see Appendix 6, Figure 12, Figure 13 and Figure 14).

CTC

The cost of a CTC investigation was estimated based on the weighted mean cost of CTC (code RD61Z) from NHS Reference Costs 2022/23.[117] In addition, the model includes the following costs associated with preparing for the test and delivering the test result: (i) a first consultation or pre-assessment 30-minute phone call with a Band 5 hospital-based nurse; (ii) bowel preparation which includes medication costs and a 30-minute phone call with a nurse, and (iii) follow-up which could be either a face-to-face appointment with a consultant (for CRC-positive cases) or a letter explaining the test results (for a diagnosis other than CRC). The total cost of a complete CTC procedure was estimated to be £492 for patients with underlying CRC and £298 for patients with a diagnosis other than CRC.

4.3.3.9. Costs of managing complications

The costs of treating complications related to diagnostic tests are summarised in Table 43.

Table 43: Costs of treating diagnostic test complications

Complication	Unit cost	Source
Bleeding (COL)*	£1,897	Assumed to require inpatient admission. NHS Reference Costs 2022/23,[117] weighted mean cost of gastrointestinal bleed with multiple, single or no intervention, non-elective long-stay and short-stay (codes FD03A to FD03H)
Perforation (COL and CTC)*	£8,120	Assumed to require inpatient admission. NHS Reference Costs 2022/23,[117] weighted mean cost of major large intestine procedures, 19 years and over, non-elective long-stay and short-stay (codes FF34A to FF34C)
Aspiration (CCE)	£2,908	Assumed to require bronchoscopy in 46% of cases, with the remainder being resolved without intervention.[137] NHS Reference Costs 2022/23,[117] weighted mean cost of therapeutic bronchoscopy, non-elective long-stay and short-stay (code DZ68Z)
Retention (CCE) – detection	£41	Assumes X-ray for patients with incomplete index CCE. NHS Reference Costs 2022/23,[117] weighted mean cost of direct access film (code DAPFI, service code 812): £41
Retention (CCE) – locate capsule	£142	Assumes patients with confirmed retention require a CT scan to provide information on capsule location. NHS Reference Costs 2022/23,[117] weighted mean cost of computerised tomography scan of more than one area (codes RD20A to RD21A, RD22Z to RD27Z)
Retention (CCE) – management	£4,164	45.95% of patients assumed to require surgery, 25.98% require endoscopy and 5.09% require medical treatment[138] (assumed to require 5 inpatient days). NHS Reference Costs 2022/23,[117] • Weighted mean cost of major large intestine procedures, 19 years and over, with CC Score 0-3+, non-elective long-stay and short-stay (codes FF34A to FF34C), • Weighted mean cost of diagnostic colonoscopy with biopsy, 19 years and over, elective, day case and outpatient procedures (code FE31Z), • General ward cost per bed day from Guest *et al.*[147] uplifted from 2016/17 to 2022/23 prices.
Lifetime cost associated with radiation-related CRC (CTC)	£29,919	Bespoke re-analysis of the MiMiC-Bowel model,[122] 2022/23 prices

CRC - colorectal cancer; CC - complications/comorbidity; CCE - colon capsule endoscopy; CTC - computed tomography colonography; COL - colonoscopy
** Where FSIG is used as a replacement or confirmatory test, the same costs are applied.*

4.3.3.10. Estimated lifetime survival, QALYs and costs for people with CRC or adenomas (long-term models 1-6)

The estimates of long-term survival, QALYs and costs for CRC or polyps in the symptomatic population and surveillance populations applied in the EAG's economic model (long-term models 1-6) are summarised in Table 44. As described in Section 4.3.2.3, these estimates are based on two sets of re-analyses of the MiMiC-Bowel cancer screening model.[111, 122] All analyses are based on a patient age

interval of 60-69 years [redacted] It should be noted that the survival estimates for people with LRAs, IBD and NSBP differ slightly between the symptomatic and surveillance populations; this is due to differences in the characteristics of patients evaluated using the MiMiC-Bowel model, and because patients in each population enter the simulation model at different time points in the modelled pathway. As shown in Table 44, delayed diagnosis results in a large survival loss and QALY loss for people with CRC, but lower costs compared with patients who are diagnosed without additional delay. This is because MiMiC-Bowel assumes a lower lifetime cost for people with stage D CRC relative to earlier CRC stages. The delayed diagnosis of AAs leads to a large survival loss and QALY loss in the surveillance population as well as additional treatment costs; the impact in the symptomatic population is estimated to be smaller. Delayed diagnoses of LRAs are estimated to result in only small impacts on survival, QALYs and costs. Further details regarding the analyses of MiMiC-Bowel can be found in Appendix 7.

4.3.3.11. Estimated lifetime survival, QALYs and costs for people with IBD or NSBP (long-term models 7, 8 and 9)

People with IBD who are diagnosed without a delay (long-term model 7) are assumed to have no excess mortality risk compared with the age- and sex-matched general population. Mean health utility for people with IBD was assumed to be 0.75, based on EQ-5D-3L estimates reported by Woehl *et al.*,[148] the relative incidence of UC and CD and disease severity as reported by Pasvol *et al.*[149] and Ghosh *et al.*[150] The annual cost of treatment for UC was estimated to be £3,084 and for CD £6,156, based on Ghosh *et al.*[150] Based on the relative proportions of IBD cases which are UC or CD (60.5% versus 39.5%),[149] the annual cost of IBD was estimated to be £4,298 (uplifted 2022/23 cost = £5,362).

People with IBD who are diagnosed following a delay (long-term model 8) are assumed to experience no excess mortality, but comparatively lower HRQoL and higher costs compared to those who are diagnosed without a delay. In line with the model developed to inform DG56,[127] the EAG's economic model assumes that 4% of patients experience additional IBD-related complications and incur a 27% reduction in HRQoL for a period of two years. The model includes an assumption that patients will incur additional treatment costs of £342 each year for two years (uplifted cost = £427). This was based on the difference in costs between severe relapse and milder forms of UC and CD reported by Ghosh *et al.*[150] These assumptions are consistent with the previous model used to inform NICE DG56.[127] As shown in Table 44, delayed diagnoses of IBD are assumed to have small impacts on QALYs and additional treatment costs.

Patients who have NSBP (long-term model 9) are assigned mortality risks from age- and sex-matched general population life tables,[123] general population EQ-5D-3L values,[126] and zero future costs.

Age-adjustment of utility values was included for all long-term models, based on Hernandez Alava *et al.*[126] [redacted]

Table 44: Discounted long-term payoffs associated with CRC and adenomas diagnosed with or without diagnostic delay

Population	Payoff	Long-term model 1 (CRC, no delay)*	Long-term model 2 (CRC, with delay)†	Long-term model 3 (AAs, no delay)	Long-term model 4 (AAs, with delay)†	Long-term model 5 (LRAs, no delay)‡	Long-term model 6 (LRAs, with delay)†§	Long-term model 7 (IBD, no delay)	Long-term model 8 (IBD, with delay)	Long-term model 9 (NSBP)
Symptomatic	LYGs	10.34	9.40	14.59	14.55	14.59	14.58	14.59	14.59	14.59
	QALYs	7.31	6.71	11.50	11.34	11.50	11.48	10.28	10.22	11.50
	Costs	£29,919	£28,222	£521	£3,259	£0	£292	£78,202	£79,057	£0
Surveillance	LYGs	13.00	10.54	14.01	13.30	14.01	13.93	14.01	14.01	14.01
	QALYs	9.32	7.77	10.93	10.31	10.93	10.86	9.77	9.71	10.93
	Costs¶	£32,199	£24,186	£661	£5,878	£190	£745	£75,118	£75,973	£0

CRC - colorectal cancer; AAs - advanced adenomas; LRAs - low-risk adenomas; IBD - inflammatory bowel disease; LYG - life year gained; QALY - quality-adjusted life year; NSBP - no significant bowel pathology

**Reweighted based on the CRC stage distribution at diagnosis. CRC stage distribution from NCRAS[124] was used for the symptomatic population. For the surveillance population, the model assumes that 50% of CRC patients detected in surveillance are Stage A and 50% are Stage B.*

† The diagnostic delay was assumed to be 8 months for CRC and 36 months for LRAs and AAs in the EAG's model, based on clinical opinion.

‡ The payoffs for the symptomatic population are assumed to be the same as payoffs in people with NSBP.

§ Whyte et al. do not report payoffs associated with additional delays for people with LRAs. Within the EAG's model, survival losses, QALY losses and additional costs associated with missed LRAs in the symptomatic population were assumed to be proportional to the ratio of the payoffs for missed diagnoses of LRAs vs AAs in the surveillance population.

¶Costs of CRC, AAs, LRAs and IBD are uplifted to 2022/23 prices.

4.3.3.12. Costs of further diagnostic tests for patients who are diagnosed following a delay (long-term models 2,4,6 and 8)

For patients with delayed diagnosis of the underlying pathology (CRC, AA, LRA or IBD), the model includes additional costs associated with further investigations used later to correct the initial misdiagnosis. The model includes the total cost of a diagnostic COL (including a GP visit cost of £49,[121] bowel preparation and follow-up visit costs) in addition to the lifetime disease management costs detailed in Table 44. This cost is applied to all late diagnoses.

4.3.4 Methods for model evaluation

The health outcomes and costs are estimated for each diagnostic imaging test (CCE, COL, CTC) in COL-eligible groups across three analysis populations (symptomatic FIT 10-100μg/g, symptomatic FIT <10μg/g and post-polypectomy surveillance). Health outcomes and costs were also estimated for CCE and CTC in the COL-ineligible group. The incremental cost-effectiveness of CCE versus COL and CTC is evaluated using fully incremental analysis based on the expectation of the mean. Results are also presented using net monetary benefit (NMB) assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained. Uncertainty was evaluated using PSA and deterministic sensitivity analyses (DSAs). PSA was undertaken using Monte Carlo sampling across 5,000 iterations. The distributions applied to each group of parameters in the model are summarised in Table 45.

Table 45: Distributions used in the EAG's probabilistic analyses

Model parameter group	Model parameter	Distribution	EAG comments
Patient characteristics	Age, proportion of females	Fixed	-
Disease prevalence	Prevalence of CRC, LRA, AA, IBD, no pathology across all populations	Dirichlet	Includes non-informative prior of 1.0 for all pathology groups
Diagnostic accuracy of CCE	Sensitivity for CRC, LRA, AA and IBD	Bivariate normal	Based on CODA samples from EAG meta-analysis
	Specificity		
Diagnostic accuracy and diagnostic COL	Sensitivity for CRC, LRA and AA	Beta	-
	Sensitivity for IBD and specificity	Fixed	Structural assumption
Diagnostic accuracy of CTC	Sensitivity for CRC, LRA and AA	Beta	-
	Sensitivity for IBD and specificity	Beta	-
Completion rate of diagnostic tests	Completion rate of CCE, COL (diagnostic), COL (therapeutic) and CTC	Beta	-
Risk of complications	Risk of bleeding, perforation, aspiration, retention and lifetime risk of radiation-related CRC	Beta	-
Mortality due to complications	Mortality due to complications related to CCE, COL (diagnostic), COL (therapeutic), CTC	Beta	-
QALY losses due to complications	QALY losses due to severe bleeding, perforation and retention	Beta	-

Model parameter group	Model parameter	Distribution	EAG comments
Costs of diagnostic tests	Costs of CCE, COL, CTC, X-ray and CT	Gamma	-
	Costs of nurse consultations	Gamma	-
	Costs of bowel preparation	Fixed	Drug costs excluded from PSA
	HCRU costs (costs of consultation before and after the test)	Gamma	-
Disease stage/ severity distribution	CRC stage distribution for FIT 10-100µg/g population and FIT <10µg/g population	Fixed	Assumption
	CRC stage distribution in surveillance population	Fixed	Assumption, varied in DSA
Estimated diagnostic delay	Additional time to diagnosis of CRC, LRA and AA	Fixed	Structural assumption - varied in DSA
Long-term model outcomes	LYGs, QALYs and costs for patients with CRC, LRA, AA, IBD and no pathology, across all populations	Gamma	-
Proportion of failed index tests repeating the same type of test during replacement	Proportion of failed CCE tests repeating CCE as a replacement test	Fixed	Structural assumption
	Proportion of failed CTC tests repeating CTC as a replacement test	Fixed	Structural assumption
	Proportion of failed index COL tests repeating COL as a replacement test	Beta	-
Proportion of incomplete CCE tests getting a X-ray	Proportion of incomplete CCE procedure receiving a post-CCE X-ray	Beta	Assumption - varied in scenario analysis
Proportion of patients with AAs who had undergone polypectomy during index/replacement test	Proportion of patients with AAs who had been treated with polypectomy during index/replacement tests	Fixed	Assumption
Proportionate use of FSIG vs COL	Proportion of replacement/confirmatory endoscopies which are FSIG vs COL	Beta	-

QALY - quality-adjusted life years; CRC - colorectal cancer; LRA - low-risk adenomas; AA - advanced adenomas; IBD - inflammatory bowel disease; COL - colonoscopy; CTC - computed tomography colonography; CT - computed tomography; CCE - colon capsule endoscopy; HCRU - health care resource use; FIT - faecal immunochemical test; CODA - convergence diagnosis and output analysis

Summary of scenario analyses undertaken

The EAG undertook a broad range of DSAs to explore the impact of alternative assumptions on the ICERs for CCE versus COL and CTC. These included the following scenarios:

- *DSA1.* All patients with an incomplete CCE test are assumed to receive a post-CCE X-ray to rule out the possibility of retention.
- *DSA2:* All CCE tests (index/replacement) are assumed to be preceded by a CT scan to assess retention risk.

- *DSA3:* The cost per CCE investigation was based on the mean cost of wireless capsule endoscopy for 19 years and over (code FE50A) from NHS Reference Costs 2022/23.[117]
- *DSA4:* CCE was assumed to be swallowed in a primary care setting rather than in secondary care. The cost of the appointment was assumed to be equivalent to that of a GP visit rather than a hospital outpatient visit (cost = £26.50 for a 30-minute appointment with a nurse with qualifications[121]).
- *DSA5:* The use of a patency capsule was assumed to be required in 14.7% of cases prior to CCE based on O'Hara *et al.*[151] The cost per PillCam patency capsule was assumed to be [redacted] This analysis applied an expected cost of patency capsules per patient receiving CCE of [redacted]. The cost of a CT scan was also included for patients receiving the patency capsule (administered prior to CCE). The risk of retention was assumed to be zero (i.e., patency capsules effectively eliminate retention risk). The costs of post-CCE X-ray were excluded.
- *DSA6:* CCE reading time was assumed to be £71.50 per procedure based on a reading time of 30 minutes (rather than 1 hour).
- *DSA7:* The prevalence of CRC, LRA and AAs in the FIT 10-100µg/g population was based on data from the Fast Track FIT study used to inform the company's model[115] (prevalence CRC, LRAs and AAs = 0.03, 0.14 and 0.04, respectively).
- *DSA8:* The sensitivity of COL for detecting CRC was based on a US population-based study of PCCRC miss rates reported by Bressler *et al.*[152] (sensitivity of COL for CRC = 0.97).
- *DSA9:* The diagnostic accuracy of CCE was based on estimates reported in a previous SLR by Spada *et al.*[100] (sensitivity for CRC = 1.0, sensitivity for LRAs = 0.86, sensitivity for AAs = 0.87, specificity = 0.95).
- *DSA10:* The diagnostic accuracy of CCE was assumed to be equivalent to COL (sensitivity for CRC = 0.94, sensitivity for LRAs = 0.87, sensitivity for AAs = 0.93, specificity = 1.00).
- *DSA11:* The diagnostic accuracy of CCE was based on sensitivity analysis 1 from the EAG's meta-analysis (sensitivity for CRC = 0.88, sensitivity for LRAs = 0.86, sensitivity for AAs = 0.88, specificity = 0.911).
- *DSA12:* The diagnostic accuracy of CTC was based on Halligan *et al.*[153] (sensitivity for CRC = 0.93, sensitivity for LRAs = 0.86, sensitivity for AAs = 0.93, specificity = 0.86).
- *DSA13:* The diagnostic accuracy of CTC was based on Rosman *et al.*[154] (sensitivity for CRC = 0.82, sensitivity for LRAs = 0.63, sensitivity for AAs = 0.82, specificity = 0.84).
- *DSA14:* The diagnostic accuracy of CCE was assumed to be equivalent to CTC (sensitivity for CRC = 0.91, sensitivity for LRAs = 0.77, sensitivity for AAs = 0.91, sensitivity for IBD = 0.84, specificity = 0.80).

- *DSA15:* The sensitivity of COL was based on Van Rijn *et al.*[113] (sensitivity for CRC = 0.98, sensitivity for LRAs = 0.74, sensitivity for AAs = 0.87).
- *DSA16:* The completion rate for CCE was assumed to be 100%.
- *DSA17:* This analysis excludes the use of FSIG as a replacement or confirmatory test (all patients receive COL instead).
- *DSA18:* Within this analysis, 60% of CTCs which are incomplete due to inadequate bowel preparation were assumed to have COL as a replacement test (the remaining 40% undergo a repeat CTC).
- *DSA19:* Patients with LRAs detected by CTC and CCE were assumed not to receive a confirmatory COL or polypectomy for a period of 1 year.
- *DSA20:* The analysis applies a less advanced stage distribution for patients with a complete index CCE within the FIT <10µg/g population, based on an assumption that current waiting times for COL in this group (estimated to be around 8 months) could be reduced by 50% if CCE was introduced. This alternative CRC stage distribution was estimated using the modelled estimates of the impact of additional time to diagnosis by Whyte *et al.*[122] and involved back-calculating the CRC stage distribution that would be required at *t*-4 months in order to reach the stage distribution applied in the EAG's base case analysis.
- *DSA21:* The diagnostic delay for missed CRCs was assumed to be 1.5 years (approximately double the base case estimate).
- *DSA22:* The diagnostic delay for missed CRCs was assumed to be 4 months (approximately half the base case estimate).
- *DSA23:* The long-term management costs for CRC and polyps were assumed to be equal to the base case estimates plus 25%.
- *DSA24:* The long-term management costs for CRC and polyps were assumed to be equal to the base case estimates minus 25%.
- *DSA25:* The CRC stage distribution in the post-polypectomy surveillance population was assumed to be 75% Stage A and 25% Stage B.
- *DSA26:* For failed index CTCs in the COL-ineligible group, non-invasive tests (CT/MRI) were used a replacement test (instead of CCE). This scenario assumes that non-invasive tests and CTC have the same diagnostic accuracy. Bowel preparation costs and test-related complications are excluded. The analysis applies a weighted cost of £181 based on a mean cost for CT of £142 (NHS Reference Costs 2022-23 [RD23Z -RD27Z]) and a mean cost for MRI of £221 (NHS Reference Costs 2022-23 [RD04Z -RD06Z]), assuming a 50% weighting for each imaging test.
- *DSA27:* The diagnostic accuracy of CCE was assumed to be equivalent to COL, and the completion rate of CCE was assumed to be 85% based on Turvill and McAlindon.[32] This represents a highly optimistic scenario for CCE.

4.3.5 Model verification and validation

The EAG undertook several measures to ensure the validity of the model.

- Peer review of the economic analysis by a modeller who was not involved in model development
- Verification and scrutiny of the executable model by two model developers
- Double-programming of the deterministic version of the implemented model
- Double-checking of the accuracy of all model inputs against sources
- Comparison of model results using point estimates of parameters and the expectation of the mean
- Comparison of mean of all probabilistic parameter samples against point estimates of parameters
- Examination of all identified sources of discrepancy
- Model testing using sensitivity analysis and use of extreme parameter values.

4.3.6 Results of the EAG's economic analysis

4.3.6.1 Central estimates of cost-effectiveness

Fully incremental results of the probabilistic and deterministic versions of the EAG's base case model for each of the six analysis populations 1a-3b are presented in Table 46 and Table 47, respectively. CEACs for each of the six analysis populations can be found in Appendix 10. Pairwise ICERs for CCE versus each comparator are provided in Appendix 11.

Within the COL-eligible groups (analysis populations 1a, 2a and 3a), the probabilistic version of the model indicates that CCE is expected to lead to small QALY losses and increased costs compared with COL; as such, CCE is expected to be dominated by COL. CTC is expected to be less effective and less expensive than COL in all populations, and is estimated to generate slightly more QALYs than CCE in the surveillance population. The ICERs for COL versus CTC are high in the symptomatic populations at £142,000 per QALY gained or higher; in the surveillance population, the ICER is more favourable at £13,788 per QALY gained. The main reasons that CCE is dominated by COL are: (i) COL is assumed to have higher sensitivity than CCE for detecting polyps and CRC which leads to slightly fewer QALYs for CCE; (ii) a large proportion ([redacted]) of CCEs are incomplete and these patients are assumed to be referred on for COL/FSIG as a replacement test, leading to increased costs, and (iii) patients in whom CCE detects significant bowel pathology (either correctly or incorrectly) are assumed to be referred on for COL/FSIG as a confirmatory test to enable biopsy or polypectomy, leading to increased costs. The deterministic version of the model also suggests that CCE is dominated by COL in all three COL-eligible populations. The CEACs indicate that the probability that CCE generates more net benefit than COL and CTC at a WTP threshold of £30,000 per QALY gained is approximately zero in all three COL-eligible populations (see Appendix 10, Figure 18, Figure 20 and Figure 22).

Within the COL-ineligible groups (analysis populations 1b, 2b and 3b), the results of the model vary between the populations. Within the symptomatic FIT 10-100µg/g and surveillance populations, the

probabilistic version of the model suggests that CCE is expected to generate slightly fewer QALYs and higher costs than CTC; as such, CCE is expected to be dominated by CTC. The main reasons for this finding are: (i) CTC is assumed to have higher sensitivity than CCE for detecting AAs and CRC which leads to slightly fewer QALYs for CCE in the symptomatic FIT 10-100µg/g and surveillance populations; (ii) the cost per CTC procedure is lower than that for CCE, and (iii) a large proportion ([redacted]) of CCEs are incomplete and these patients are assumed to require CTC as a replacement test leading to increased costs. Within the symptomatic FIT <10µg/g population, the model suggests that CCE generates slightly more QALYs and incurs higher costs compared to CTC; the ICER is expected to be in excess of £713,000 per QALY gained. The results of the deterministic version of the model are similar to those obtained from the probabilistic version of the model, with the exception that CCE versus CTC in the FIT 10-100µg/g population moves from being dominated to having an ICER of around £7.21million per QALY gained. The CEACs indicate that the probability that CCE generates more net benefit than CTC at a WTP threshold of £30,000 per QALY gained is approximately zero in all three COL-ineligible populations (see Appendix 10, Figure 19 and Figure 21 and Figure 23).

Table 46: Central estimates of cost-effectiveness – CCE versus COL and/or CTC, probabilistic, ranked by QALYs

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	Incremental cost per QALY gained	INMB WTP=£20,000/ QALY (CCE vs comparator)	INMB WTP=£30,000/ QALY (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
COL	14.52	11.3517	£5,090	0.00	0.0023	£324	£142,565	-£356	-£373
CCE	14.51	11.3501	£5,413	-	-	-	**Dominated**	-	-
CTC	14.52	11.3494	£4,766	-	-	-	-	-£634	-£628
Population 1b: Symptomatic, FIT 10-100µg/g, COL-ineligible									
CTC	14.52	11.3494	£4,771	0.00	0.0001	-£576	Dominating	-£578	-£579
CCE	14.51	11.3493	£5,347	-	-	-	**Dominated**	-	-
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
COL	14.60	11.4689	£2,283	0.00	0.0019	£376	£200,840	-£286	-£290
CCE	14.60	11.4685	£2,559	-	-	-	**Dominated**	-	-
CTC	14.60	11.4671	£1,907	-	-	-	-	-£624	-£610
Population 2b: Symptomatic, FIT <10µg/g, COL-ineligible									
CCE	14.60	11.4678	£2,476	0.00	0.0008	£566	**£713,959**	-	-
CTC	14.60	11.4670	£1,910	-	-	-	-	-£550	-£542
Population 3a: Surveillance (post-polypectomy), COL-eligible									
COL	14.01	10.8882	£2,028	0.01	0.0061	£84	£13,788	-£714	-£798
CTC	14.00	10.8821	£1,944	-	-	-	-	-£676	-£700
CCE	14.00	10.8797	£2,573	-	-	-	**Dominated**	-	-
Population 3b: Surveillance (post-polypectomy), COL-ineligible									
CTC	14.00	10.8818	£1,955	0.01	0.0041	-£626	Dominating	-£708	-£749
CCE	14.00	10.8777	£2,581	-	-	-	**Dominated**	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. - incremental

Table 47: Central estimates of cost-effectiveness – CCE versus COL and/or CTC, deterministic, ranked by QALYs

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	Incremental cost per QALY gained	INMB WTP=£20,000/ QALY (CCE vs comparator)	INMB WTP=£30,000/ QALY (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
COL	14.50	11.3583	£5,073	0.00	0.0023	£323	£140,932	-£349	-£364
CCE	14.50	11.3568	£5,392	-	-	-	**Dominated**	-	-
CTC	14.50	11.3560	£4,750	-	-	-	-	-£626	-£618
Population 1b: Symptomatic, FIT 10-100µg/g, COL-ineligible									
CCE	14.50	11.3560	£5,326	0.00	0.0001	£571	**£7,208,331**	-	-
CTC	14.50	11.3560	£4,755	-	-	-	-	-£570	-£569
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
COL	14.59	11.4800	£2,177	0.00	0.0019	£377	£201,404	-£279	-£282
CCE	14.59	11.4796	£2,448	-	-	-	**Dominated**	-	-
CTC	14.59	11.4781	£1,800	-	-	-	-	-£618	-£603
Population 2b: Symptomatic, FIT <10µg/g, COL-ineligible									
CCE	14.59	11.4790	£2,365	0.00	0.0009	£562	**£632,836**	-	-
CTC	14.59	11.4781	£1,803	-	-	-	-	-£544	-£535
Population 3a: Surveillance (post-polypectomy), COL-eligible									
COL	14.00	10.9097	£1,801	0.01	0.0062	£82	£13,356	-£689	-£764
CTC	13.99	10.9036	£1,719	-	-	-	-	-£648	-£662
CCE	13.99	10.9022	£2,339	-	-	-	**Dominated**	-	-
Population 3b: Surveillance (post-polypectomy), COL-ineligible									
CTC	13.99	10.9034	£1,729	0.00	0.0032	-£618	Dominating	-£681	-£713
CCE	13.98	10.9002	£2,347	-	-	-	**Dominated**	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. – incremental

4.3.6.2 Model-predicted intermediate outcomes

Table 48 presents a summary of model-predicted intermediate clinical outcomes in terms of the number of COLs/FSIGs required, pathology detected, pathology missed and complications for each diagnostic testing pathway in the COL-eligible population. The values shown in the table are scaled up to a population size of 1,000 patients tested to aid interpretation. The model suggests that CCE is expected to lead to substantial reductions in the number of COLs/FSIGs required compared with the COL-based pathway – these reductions are estimated to be approximately 46%, 50% and 32% in the symptomatic FIT 10-100µg/g, symptomatic FIT <10µg/g and surveillance populations, respectively. [redacted] Based on the model, CCE is predicted to lead to more subsequent COLs/FSIGs compared with the CTC-based pathway. This is because all patients with an incomplete index test are assumed to require COL/FSIG and the probability that CTC will be incomplete is substantially lower than the probability that a CCE will be incomplete (2% versus [redacted]). As a consequence of the modelled diagnostic accuracy of the tests, CCE is predicted to miss more polyps and/or CRCs compared with COL – this is the main reason that CCE is predicted to generate fewer QALYs than COL. Compared with CTC, the model indicates that CCE will lead to more LRAs and fewer AAs/CRCs being detected – the underlying prevalence of CRC, polyps and IBD in each analysis population determines whether the incremental QALYs for CCE versus CTC are positive or negative. As highlighted in Table 46, the QALY losses resulting from CCE missing polyps are very small in all COL-eligible populations.

Table 49 presents model-predicted intermediate outcomes for the COL-ineligible subgroups. The model suggests that compared with the CTC-based pathway, CCE will lead to a small reduction in the number of people being referred for COL/FSIG – these reductions are estimated to be approximately, 8%, 10% and 2% in the symptomatic FIT 10-100µg/g, symptomatic FIT <10µg/g and surveillance populations, respectively. Corresponding estimates of COL capacity spared in for people declining COL were not available from the NHSE CCE Pilot Study.[40] As a consequence of the diagnostic test sensitivity estimates applied in the model, the model predicts that compared with CTC, CCE will lead to more LRAs and fewer AAs/CRCs being detected; where applicable, the QALY losses resulting from CCE missing polyps are very small in the COL-ineligible analysis populations.

Table 48: Model-predicted clinical and economic outcomes per 1,000 patients – CCE versus COL and/or CTC, deterministic, in COL eligible groups

Outcome per person	1a: Symptomatic, FIT 10-100µg/g, COL-eligible					2a: Symptomatic, FIT <10µg/g, COL-eligible					3a: Surveillance (post-polypectomy), COL-eligible				
	Absolute			Incremental		Absolute			Incremental		Absolute			Incremental	
	CCE	CTC	COL	CCE vs CTC	CCE vs COL	CCE	CTC	COL	CCE vs CTC	CCE vs COL	CCE	CTC	COL	CCE vs CTC	CCE vs COL
COLs/FSIGs undertaken*	576.50	452.45	1063.10	124.05	-486.60	531.36	394.79	1055.49	136.57	-524.13	733.60	631.81	1081.85	101.79	-348.26
COLs undertaken*	374.08	293.59	1051.42	80.49	-677.33	340.65	253.10	1046.28	87.55	-705.63	572.14	492.75	1070.40	79.39	-498.27
Follow-up COLs/FSIGs	271.57	432.45	33.28	-160.88	238.29	226.43	374.79	25.67	-148.36	200.76	428.67	611.81	52.03	-183.14	376.64
No. people with CRC detected	17.87	18.60	19.04	-0.73	-1.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
No. people with CRC missed	2.52	1.78	1.35	0.73	1.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
No. people with AAs detected	96.39	100.53	102.26	-4.14	-5.87	51.95	54.18	55.12	-2.23	-3.17	185.72	193.69	197.03	-7.97	-11.32
No. people with AAs missed	13.80	9.66	7.92	4.14	5.87	7.44	5.21	4.27	2.23	3.17	26.58	18.61	15.27	7.97	11.32
No. people with LRAs detected	182.48	167.65	186.94	14.83	-4.46	197.98	181.89	202.83	16.09	-4.84	400.91	368.33	410.72	32.58	-9.81
No. people with LRAs missed	34.43	49.25	29.96	-14.83	4.46	37.35	53.44	32.51	-16.09	4.84	75.64	108.21	65.83	-32.58	9.81
No. people with IBD detected	36.16	34.23	36.05	1.92	0.10	10.74	10.17	10.71	0.57	0.03	2.16	2.04	2.15	0.11	0.01
No. people with IBD missed	4.40	6.33	4.51	-1.92	-0.10	1.31	1.88	1.34	-0.57	-0.03	0.26	0.38	0.27	-0.11	-0.01
No. complications	9.95	3.37	1.31	6.57	8.63	9.70	3.01	1.25	6.69	8.45	12.15	6.31	1.57	5.83	10.58

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; QALY - quality-adjusted life year; LRA - low-risk adenoma; AA - advanced adenoma; IBD - inflammatory bowel disease; AE - adverse event

** Includes index, replacement and confirmatory tests. Excludes false-negatives.*

Table 49: Model-predicted clinical and economic outcomes per 1,000 patients – CCE versus COL and/or CTC, deterministic, in COL ineligible groups

Outcome per person	1b: Symptomatic, FIT 10-100µg/g, COL-ineligible			2b: Symptomatic, FIT <10µg/g, COL-ineligible			3b: Surveillance (post-polypectomy), COL-ineligible		
	Absolute		Incremental	Absolute		Incremental	Absolute		Incremental
	CCE	CTC	CCE vs CTC	CCE	CTC	CCE vs CTC	CCE	CTC	CCE vs CTC
COLs/FSIGs undertaken*	402.94	439.97	-37.03	341.33	381.15	-39.82	612.90	623.58	-10.68
COLs undertaken*	261.46	285.49	-24.03	218.82	244.35	-25.53	478.00	486.33	-8.33
Follow-up COLs/FSIGs†	402.94	439.97	-37.03	341.33	381.15	-39.82	612.90	623.58	-10.68
No. people with CRC detected	17.73	18.57	-0.84	0.00	0.00	0.00	0.00	0.00	0.00
No. people with CRC missed	2.66	1.82	0.84	0.00	0.00	0.00	0.00	0.00	0.00
No. people with AAs detected	95.82	100.35	-4.54	51.65	54.09	-2.45	184.62	193.36	-8.74
No. people with AAs missed	14.37	9.83	4.54	7.74	5.30	2.45	27.68	18.94	8.74
No. people with LRAs detected	176.13	167.49	8.64	191.09	181.72	9.37	386.96	367.98	18.98
No. people with LRAs missed	40.78	49.41	-8.64	44.24	53.61	-9.37	89.59	108.57	-18.98
No. people with IBD detected	35.56	34.23	1.33	10.56	10.17	0.39	2.12	2.04	0.08
No. people with IBD missed	5.00	6.33	-1.33	1.49	1.88	-0.39	0.30	0.38	-0.08
No. complications	10.65	3.43	7.21	10.31	3.07	7.24	13.73	6.43	7.30

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; QALY - quality-adjusted life year; LRA - low-risk adenoma; AA - advanced adenoma; IBD - inflammatory bowel disease; AE - adverse events; NMB - net monetary benefit

** Includes index, replacement and confirmatory tests. Excludes false-negatives*

†The number of follow-up COLs/FSIGs and total COLs/FSIGs undertaken are the same because no patients are assumed to undergo COL/FSIG as a replacement test in these populations.

4.3.6.3 Breakdown of model-predicted costs

A breakdown of the model-predicted costs per person tested in the COL-eligible and COL-ineligible populations is shown in Table 50 and Table 51, respectively. In all populations, the main driver of incremental costs for CCE versus each comparator is the short-term diagnostic test costs. These costs are predicted to be higher for CCE than the comparators because a large proportion of patients undergoing CCE will require a further test, either because the index CCE was incomplete, or because the CCE identified relevant bowel pathology requiring subsequent COL/FSIG and biopsy or polypectomy. Differences in costs related to complications and long-term disease management between the options are predicted to be small.

Table 50: Breakdown of model-predicted costs in COL-eligible populations

Costs per person	1a: Symptomatic, FIT 10-100µg/g, COL-eligible					2a: Symptomatic, FIT <10µg/g, COL-eligible					3a: Surveillance (post-polypectomy), COL-eligible				
	Absolute			Incremental		Absolute			Incremental		Absolute			Incremental	
	CCE	CTC	COL	CCE vs CTC	CCE vs COL	CCE	CTC	COL	CCE vs CTC	CCE vs COL	CCE	CTC	COL	CCE vs CTC	CCE vs COL
Short-term costs															
Diagnostic tests	£1,296	£672	£1,067	£625	£229	£1,252	£615	£1,059	£637	£193	£1,470	£866	£1,093	£603	£377
Bowel preparation	£74	£59	£44	£15	£30	£72	£57	£43	£15	£29	£80	£66	£44	£14	£35
HCRU costs	£29	£29	£29	£0	£0	£25	£25	£25	£0	£0	£25	£25	£25	£0	£0
AE management	£36	£11	£5	£25	£30	£35	£10	£5	£25	£30	£41	£17	£6	£23	£35
Long-term costs															
Lifetime disease management	£3,887	£3,882	£3,871	£4	£15	£1,005	£1,004	£995	£1	£10	£593	£570	£529	£23	£64
Diagnostic test	£70	£85	£56	-£15	£14	£59	£77	£48	-£18	£10	£130	£162	£103	-£31	£27
CRC related to ionising radiation exposure (CTC)	£0	£12	£1	-£12	-£1	£0	£12	£1	-£12	-£1	£0	£12	£1	-£12	-£1
Total costs	£5,392	£4,750	£5,073	£642	£319	£2,448	£1,800	£2,177	£648	£271	£2,339	£1,719	£1,801	£620	£538

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; HCRU – health care resource use; AE - adverse events; CRC - colorectal cancer

Table 51: Breakdown of model-predicted costs in COL-ineligible populations

Costs per person	1a: Symptomatic, FIT 10-100µg/g, COL-ineligible			2a: Symptomatic, FIT <10µg/g, COL-ineligible			3a: Surveillance (post-polypectomy), COL-ineligible		
	Absolute		Incremental	Absolute		Incremental	Absolute		Incremental
	CCE	CTC	CCE vs CTC	CCE	CTC	CCE vs CTC	CCE	CTC	CCE vs CTC
Short-term costs									
Diagnostic test	£1,206	£675	£531	£1,146	£617	£529	£1,430	£874	£556
Bowel preparation	£80	£60	£20	£77	£57	£20	£88	£67	£21
HCRU	£29	£29	£0	£25	£25	£0	£25	£25	£0
AE management	£37	£11	£27	£37	£10	£27	£45	£18	£27
Long-term costs									
Lifetime disease management	£3,890	£3,883	£7	£1,008	£1,005	£4	£607	£572	£35
Diagnostic test	£80	£86	-£6	£68	£77	-£9	£149	£162	-£13
CRC related to ionising radiation exposure (CTC)	£4	£12	-£8	£4	£12	-£8	£4	£12	-£8
Total costs	£5,326	£4,755	£571	£2,365	£1,803	£562	£2,347	£1,729	£618

CCE - colon capsule endoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; HCRU – health care resource use; AE - adverse events; CRC - colorectal cancer

4.3.6.4 Deterministic sensitivity analysis results

The results of the DSAs for the COL-eligible and COL-ineligible populations are presented in Table 52 and Table 53, respectively. Within the COL-eligible groups (analysis populations 1a, 2a and 3a, Table 52), CCE is consistently dominated by COL, except for some scenarios in which alternative estimates of the diagnostic test accuracy of CCE are applied (DSAs 9, 10 and 27). However, in these scenarios, the ICER for CCE versus COL remains in excess of £389,000 per QALY gained. Consistent with the base case analyses, the ICERs for COL remain high in the symptomatic populations and low in the surveillance population across the majority of DSAs. Within the COL-ineligible groups (analysis populations 1b, 2b and 3b, Table 53), CCE is expected to be dominated by CTC in the surveillance population in most scenarios, except for some analyses in which alternative estimates of the diagnostic test accuracy of CCE or CTC are applied (DSAs 10, 11, 13, 14 and 27). The ICER remains in excess of £66,000 per QALY gained across all of these scenarios. In the symptomatic populations, CCE generates slightly more QALYs and incurs additional costs compared to CTC in most scenarios; the lowest ICER for CCE versus CTC in these populations is estimated to be greater than £204,000 per QALY gained (DSA27).

Table 52: Deterministic sensitivity analyses – CCE versus COL and/or CTC, fully incremental ICERs, in COL-eligible groups

No.	Scenario	1a: Symptomatic, FIT 10-100µg/g, COL-eligible			2a: Symptomatic, FIT <10µg/g, COL-eligible			3a: Surveillance (post-polypectomy), COL-eligible		
		CCE	COL	CTC	CCE	COL	CTC	CCE	COL	CTC
-	Base case (deterministic)	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
1	Plain X-ray for all incomplete CCE tests	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
2	Pre-test CT scan for all CCEs	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
3	CCE cost = £828.36	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
4	CCE given in primary care	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
5	Patency capsule costs included	Dominated	[redacted]	-	Dominated	[redacted]	-	Dominated	[redacted]	-
6	CCE reading time = 30 minutes	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
7	Prevalence based on FastTrack FIT	Dominated	£200,816	-	Dominated	£201,404	-	Dominated	£13,356	-
8	COL miss rate from Bressler *et al.*[152]	Dominated	£122,441	-	Dominated	£201,404	-	Dominated	£13,356	-
9	CCE diagnostic accuracy from Spada *et al.*[155]	£4,445,385	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
10	CCE diagnostic accuracy equivalent to COL	£1,152,673	£140,932	-	£975,481	£201,404	-	£1,170,900	£13,356	-
11	CCE diagnostic accuracy from EAG meta-analysis SA1	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
12	CTC diagnostic accuracy from Halligan *et al.*[153]	Dominated	£241,221	-	Dominated	£299,936	-	Dominated	£95,446	-
13	CTC diagnostic accuracy from Rosman *et al.*[154]	Dominated	£58,585	-	Dominated	£119,480	-	Dominated	Dominating	Dominated
14	CCE diagnostic accuracy equivalent to CTC	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
15	COL miss rates from Van Rijn *et al.*[113]	Dominated	£106,659	-	Dominated	£217,593	-	Dominated	£13,492	-
16	CCE completion rate = 100%	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
17	COL used instead of FSIG	Dominated	£132,520	-	Dominated	£192,134	-	Dominated	£10,644	-
18	CTC repeated for 40% of incomplete CTCs	Dominated	£140,653	-	Dominated	£201,061	-	Dominated	£13,266	-
19	LRAs detected by CCE/CTC not referred for 1 year	Dominated	£241,428	-	Dominated	£351,299	-	Dominated	£74,174	-
20	Improved CRC stage dist. for CCE	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
21	Diagnostic delay for missed CRC = 1.5 years	Dominated	£124,956	-	Dominated	£201,404	-	Dominated	£13,356	-
22	Diagnostic delay for missed CRC = 4 months	Dominated	£148,305	-	Dominated	£201,404	-	Dominated	£13,356	-
23	Long-term costs for polyps and CRCs + 25%	Dominated	£138,683	-	Dominated	£198,751	-	Dominated	£11,238	-
24	Long-term costs for polyps and CRCs - 25%	Dominated	£143,181	-	Dominated	£204,058	-	Dominated	£15,475	-
25	Surveillance CRC dist. = 75% stage A, 25% stage B	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
26	CT/MRI used after failed index CTC (COL-ineligible)	Dominated	£140,932	-	Dominated	£201,404	-	Dominated	£13,356	-
27	CCE diagnostic accuracy equivalent to COL, CCE completion rate = 85%	£608,006	£140,932	-	£389,765	£201,404	-	£1,190,585	£13,356	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FSIG - flexible sigmoidoscopy; CT - computed tomography; MRI - magnetic resonance imaging; SA - sensitivity analysis; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; dist. - distribution

Table 53: Deterministic sensitivity analyses – CCE versus CTC, fully incremental ICERs, in COL-ineligible groups

No.	Scenario	1b: Symptomatic, FIT 10-100µg/g, COL-ineligible		2b: Symptomatic, FIT <10µg/g, COL-ineligible		3b: Surveillance (post-polypectomy), COL-ineligible	
		CCE	CTC	CCE	CTC	CCE	CTC
-	Base case (deterministic)	£7,208,331	-	£632,836	-	Dominated	Dominating
1	Plain X-ray for all incomplete CCE tests	£7,286,818	-	£639,848	-	Dominated	Dominating
2	Pre-test CT scan for all CCEs	£8,957,809	-	£789,118	-	Dominated	Dominating
3	CCE cost = £828.36	£8,360,712	-	£735,779	-	Dominated	Dominating
4	CCE given in primary care	£6,008,392	-	£525,645	-	Dominated	Dominating
5	Patency capsule costs included	[redacted]	-	[redacted]	-	Dominated	Dominating
6	CCE reading time = 30 minutes	£6,324,445	-	£553,879	-	Dominated	Dominating
7	Prevalence based on FastTrack FIT	£2,491,007	-	£632,836	-	Dominated	Dominating
8	COL miss rate from Bressler *et al.*[152]	£7,208,331	-	£632,836	-	Dominated	Dominating
9	CCE diagnostic accuracy from Spada *et al.*[155]	£341,736	-	£493,506	-	Dominated	Dominating
10	CCE diagnostic accuracy equivalent to COL	£292,452	-	£343,936	-	£117,118	-
11	CCE diagnostic accuracy from EAG meta-analysis SA1	£697,981	-	£471,935	-	£1,399,401	-
12	CTC diagnostic accuracy from Halligan *et al.*[153]	Dominated	Dominating	£1,070,351	-	Dominated	Dominating
13	CTC diagnostic accuracy from Rosman *et al.*[154]	£254,486	-	£312,748	-	£66,672	-
14	CCE diagnostic accuracy equivalent to CTC	£531,542	-	£547,098	-	£556,597	-
15	COL miss rates from Van Rijn *et al.*[113]	£7,208,331	-	£632,836	-	Dominated	Dominating
16	CCE completion rate = 100%	£2,165,063	-	£305,665	-	Dominated	Dominating
17	COL used instead of FSIG	£7,186,859	-	£630,728	-	Dominated	Dominating
18	CTC repeated for 40% of incomplete CTCs	£7,146,953	-	£630,405	-	Dominated	Dominating
19	LRAs detected by CCE/CTC not referred for 1 year	Dominated	Dominating	£699,498	-	Dominated	Dominating
20	Improved CRC stage dist. for CCE	£7,208,331	-	£632,836	-	Dominated	Dominating
21	Diagnostic delay for missed CRC = 1.5 years	Dominated	Dominating	£632,836	-	Dominated	Dominating
22	Diagnostic delay for missed CRC = 4 months	£1,883,371	-	£632,836	-	Dominated	Dominating
23	Long-term costs for polyps and CRCs + 25%	£7,209,860	-	£631,654	-	Dominated	Dominating
24	Long-term costs for polyps and CRCs - 25%	£7,206,803	-	£634,019	-	Dominated	Dominating
25	Surveillance CRC dist. = 75% stage A, 25% stage B	£7,208,331	-	£632,836	-	Dominated	Dominating
26	CT/MRI used after failed index CTC (COL-ineligible)	£11,594,497	-	£648,745	-	Dominated	Dominating
27	CCE diagnostic accuracy equivalent to COL, CCE completion rate = 85%	£204,720	-	£238,668	-	£83,228	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FSIG – flexible sigmoidoscopy; CT - computed tomography; MRI - magnetic resonance imaging; SA - sensitivity analysis; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; dist. - distribution

4.4 Discussion

4.4.1 Main conclusions of the EAG's review and independent health economic model

The EAG undertook a systematic review of economic evaluations comparing CCE using PillCam COLON 2 versus other diagnostic tests for the detection of colorectal polyps or CRC in people with symptoms of CRC and/or in people who are due to have a post-polypectomy surveillance COL. The review identified only one existing full economic evaluation (Palimaka *et al.*[104]). This study suggested that compared with CTC, CCE leads to small gains in survival due to the avoidance of FNs and additional costs; however, owing to problems in the reporting of the main results of this study, its economic conclusions are not fully clear. The EAG's systematic searches also identified two previous costing analyses on the use of CCE versus COL in Scotland undertaken by the SHTG.[105, 106] These studies did not meet the inclusion criteria for the EAG's review but were included for completeness. The updated 2024 SHTG costing analysis suggests that compared with COL, CCE is expected to result in additional costs in the surveillance population and small cost savings per person tested in symptomatic FIT-positive and FIT-negative populations. Key parameters applied in this updated cost analysis were not included in the report and so it was not possible for the EAG to provide a detailed critique.

During the appraisal process, the manufacturer of PillCam COLON 2 (Medtronic Ltd.) shared an unpublished manuscript detailing a model-based cost and resource use analysis of CCE versus COL and CCE versus CTC in the symptomatic FIT 10-100µg/g population.[107] This analysis did not meet the eligibility criteria for the EAG's review as it was not a full economic evaluation, but the study was included for completeness.

[redacted]

The EAG developed a *de novo* economic model to assess the incremental cost-effectiveness of CCE using PillCam COLON 2 versus COL and CTC in the three main analysis populations listed in the

NICE scope:[35] (i) people with symptoms suggestive of CRC with a FIT score of 10-100µg/g; (ii) people with symptoms suggestive of CRC with a FIT score of <10µg/g and (iii) people who are due to have a post-polypectomy surveillance COL at 3-years because of high-risk findings at their baseline COL. Separate model analyses were conducted within each analysis population to reflect differences in the diagnostic pathways for people who are willing and able to undergo COL and for people who initially decline COL (denoted as "COL-eligible" and "COL-ineligible" subgroups, respectively). The diagnostic pathways included in the model were informed by clinical opinion and long-term outcomes and costs were estimated through re-analyses of the MiMiC-Bowel screening model. Key model parameters were informed by the NHSE CCE Pilot Study, meta-analyses of the diagnostic accuracy of CCE, CTC and COL, systematic reviews of test complications, routine cost sources, other literature and assumptions. A wide range of sensitivity analyses were conducted to explore the impact of alternative assumptions and evidence sources on the model results.

The EAG's economic model suggests that compared with the COL-based pathway, CCE is expected to lead to substantial reductions in the number of people undergoing COL/FSIG in all three main analysis populations (symptomatic FIT 10-100µg/g, symptomatic FIT <10µg/g and surveillance groups). Compared with the CTC-based pathway, CCE is expected to result in more subsequent COLs/FSIGs in COL-eligible populations and slightly fewer subsequent COLs/FSIGs in COL-ineligible populations. CCE is expected to be more expensive than both COL- and CTC-based pathways. Given the model assumptions regarding diagnostic test accuracy, CCE is expected to lead to small QALY losses versus COL in all analysis populations. Whether CCE results in positive or negative incremental QALYs versus CTC varies across the populations according to the prevalence of LRAs, AAs and CRC, although these differences are very small regardless of the direction of effect. Across all analyses, CCE is expected to be dominated or to have a very high ICER compared with COL and CTC. The ICERs for COL versus CTC are high for symptomatic patients and low for surveillance patients. The main reason driving the higher incremental cost for CCE is the cost of the CCE together with the additional costs of necessary subsequent luminal investigation, either because the index CCE was incomplete or because significant bowel pathology is identified by CCE and subsequent biopsy or polypectomy via COL/FSIG is required. These general findings hold across the range of scenario analyses conducted using the EAG's model. Whilst the EAG did not have access to the model described in the company's manuscript, it is likely that the inclusion of [redacted] observed in the NHSE CCE Pilot Study in this model would lead to similar economic conclusions as those based on the EAG's analysis. Overall, the model suggests that the introduction of CCE in routine NHS practice would increase costs and reduce societal health as a consequence of some polyps being missed, but would free up capacity for constrained endoscopy services. The relative importance of these issues should be considered by decision-makers.

4.4.2 Strengths and limitations of the EAG's economic analysis

The EAG's economic analysis is subject to several strengths:

- The economic analysis is consistent with the NICE Reference Case and aligns with the final NICE scope.[35]
- The diagnostic pathways included in the short-term model for patients who are willing or unwilling to undergo COL were based on detailed discussions with three clinical experts (MK, KM and JT).
- The diagnostic accuracy of CCE for detecting polyps and CRC was informed by the EAG's meta-analysis of diagnostic accuracy studies (see Section 3.3.2.2). The test characteristics of COL and CTC were based on published meta-analyses.[130] Where available, risks of complications resulting from CCE and other diagnostic tests were also informed by published systematic reviews.[137-140]
- The EAG's model uses data from the NHSE CCE Pilot Study[40] to inform estimates of the prevalence of significant bowel pathology (polyps, CRCs and IBD) in each of the three main analysis populations. This study aligns directly with the populations listed in the final scope for the appraisal.[35] In addition, the use of data from the pilot study on patients who were referred for COL/FSIG after a CCE means that the polyps included in the model only relate to those which were deemed to be of sufficient clinically significance for referral for further investigation. Data from the pilot are also used to inform the CCE completion rate which is a key model parameter. The pilot study was also used to inform assumptions about the proportion of patients who undergo FSIG or COL following CCE (or CTC).
- [redacted]
- Long-term health outcomes and costs for each bowel pathology group, including the impacts of delayed diagnosis, were estimated from re-analyses of the patient-level MiMiC-Bowel screening model.[111, 122] MiMiC-Bowel is an updated and more sophisticated version of the economic model which was previously used by the National Screening Committee to inform decisions about the economic value and feasibility of alternative CRC screening options in England.[116] The outputs of the MiMiC-Bowel model were also used to inform long-term costs and health outcomes for the economic model used to inform DG56.[23]
- A comprehensive range of sensitivity analyses were conducted using the EAG's model to explore key areas of uncertainty, including diagnostic test accuracy, test completion rates, prevalence, the setting for CCE and the use of patency capsules and other measures to mitigate the risks of retention.

The EAG's economic analyses are subject to several limitations which should be borne in mind when interpreting the results:

- The EAG's model defines risk due to the presence of colorectal polyps in terms of two discrete categories – low- and high-risk. The model does not include a separate intermediate-risk group. In addition, the model considers people rather than individual polyps. This approach was taken because the MiMiC-Bowel model, which is used to quantify the health outcomes and costs associated with having diagnosed/undiagnosed polyps and CRC, is also based on states for individuals with polyps who are defined as low- and high-risk. MiMiC-Bowel defines high-risk as people with at least three small adenomas or at least one adenoma of size >10mm. In addition, the EAG's model assumes that for CCE, the estimate of sensitivity for ≥6mm polyps corresponds to the detection of polyps classed as low-risk and the estimate of sensitivity for ≥10mm polyps applies to the detection of polyps classed as high-risk. These definitions are not fully consistent, and the direction of this bias is unclear. [redacted]
- Whilst highly relevant to the decision problem, the data from the NHSE CCE Pilot Study are subject to some limitations. Specifically, several additional assumptions were required in order to use the data on COL/FSIG confirmed diagnoses in referred patients to estimate the underlying prevalence of significant bowel pathology across each of the three main analysis populations. These adjustments were informed by the Pilot Study data on CCE-detected yield as well as external estimates of diagnostic test sensitivity. The resulting estimates of underlying prevalence should be considered uncertain.
- The data available from the EAG's systematic review of diagnostic test accuracy were insufficient to estimate the sensitivity of CCE in people with <5mm polyps or with 6-9mm polyps. Instead, the EAG's model applies the meta-analysis estimate of the sensitivity of CCE for detecting ≥6mm polyps to all <10mm polyps in the model. This assumption might overestimate the ability of CCE to detect smaller lower-risk polyps. In addition, as discussed in Section 3.4, the studies included in the EAG's meta-analysis included mixed populations of patients which do not correspond well to the populations defined in the final NICE scope.[35] This leads to further uncertainty. However, the inclusion of alternative estimates of the diagnostic accuracy of CCE, COL and CTC did not change the overall economic conclusions for CCE.
- Estimates of the long-term consequences of additional delays in the diagnosis of LRAs in the symptomatic population were not available from the re-analysis conducted by Whyte *et al.*[122] As such, the EAG's model draws on the estimates from the modelled surveillance population

to inform these missing parameters. The true impact of missed LRAs on long-term outcomes is uncertain, particularly for symptomatic patients.

- The EAG's model assumes that all polyps identified by COL or FSIG would be removed at the point of detection, or in the case of "complex polyps", during a subsequent COL/FSIG procedure. The model also assumes that all people with significant polyps detected by other tests would be referred for and would undergo COL/FSIG and polypectomy. In reality, clinical decision-making is more complex and nuanced, requiring clinicians to weigh up the anticipated benefits of reducing future cancer risk through polypectomy, taking into account the patient's age and level of fitness, against the small but serious risks of complications associated with invasive endoscopy. The EAG's model is likely to overestimate the benefits of detecting polyps using CCE and CTC because it assumes that all referred patients would be willing and able to undergo polypectomy or biopsy.
- The model does not differentiate between the risks of complications for COL and FSIG, although evidence suggests that the risk of perforation for FSIG is approximately 50% of that for COL.[156] Additional model testing undertaken by the EAG indicates that including lower risks for patients having FSIG has virtually no impact on the model results.
- [redacted] These additional reading time costs are not included in the EAG's base case model because the NHS Reference Costs should reflect the full cost of providing the procedure. However, the EAG undertook additional model testing whereby the cost of 20 minutes of radiologist reading time was included; the economic conclusions for CCE remained unchanged in all analysis populations.
- Some older or frail patients may not be fit enough to undergo COL. These patients are not reflected in any of the analyses undertaken using the EAG's model. The role of CCE in older or frail patients where future subsequent polypectomy, biopsy or surgery is not possible is likely to be limited because CCE involves more intensive bowel preparation and is more expensive than other alternative diagnostic options such as CTC and CT.
- As described in the final protocol for the appraisal,[39] the EAG intended to quantify the anticipated impact of CCE on resource constraints through the estimation of reductions in the need for specific investigations such as COL and the time spent waiting for these investigations. The EAG's model incorporates estimates of the negative health consequences of additional delays in diagnosis in people who are missed by the index/replacement test as part of its structure. The model has also been used to predict expected reductions in the need for COL/FSIG following CCE in the COL-eligible and COL-ineligible groups (see Table 48 and

Table 49, respectively). However, estimating the extent to which CCE might reduce patient waiting times is particularly challenging. During the appraisal, the EAG's clinical advisors commented that waiting times are typically around 30-40 weeks for patients with symptoms and a FIT of <10µg/g, whereas those with symptoms and a FIT of 10-100µg/g are referred under the FDS which aims to ensure that patients with suspected cancer are diagnosed or have cancer ruled out within 28 days. The EAG's clinical advisors commented that in the FIT<10µg/g group, the delays tend to relate to the period from GP referral to the patient being seen in a secondary care clinic, rather than delays in accessing endoscopy after being assessed in clinic. It is unclear whether introducing CCE would reduce these waiting times, and if so, whether this would lead to improvements in health outcomes for these patients. [redacted] As shown in DSA20 (Table 52 and Table 53), including this shorter waiting time for CCE has no impact on the model results. It is possible that reducing the need for COL in the symptomatic and surveillance patients included in the scope of this appraisal would release endoscopy capacity and reduce waiting times for other patients requiring COL; however, quantifying the health benefits of redirecting spared endoscopy capacity to other patient groups is beyond the scope of this assessment.

5 DISCUSSION

5.1 Statement of principal findings

5.1.1 Clinical effectiveness – principal findings

Clinical data were included across 3 evidence types: (i) diagnostic test accuracy studies to provide evidence on the sensitivity and specificity of CCE; (ii) diagnostic yield studies to provide estimates of prevalence and capacity spared, and (iii) patient preference studies. Diagnostic test accuracy estimates from four small studies with mixed populations (with between 11% and 64% of the patients in-scope) were synthesised. Estimated sensitivity and specificity for polyps of any size (n=2)[46, 60] were 0.78 (95% CrI: 0.51-0.90) and 0.60 (95% CrI: 0.27-0.88), respectively; for ≥6mm polyps (n=4)[42, 46, 75, 77] 0.83 (95% CrI: 0.70-0.91) and 0.69 (95% CrI: 0.52-0.81), respectively; and for ≥10mm polyps (n=4)[42, 46, 75, 77] 0.85 (95% CrI: 0.70-0.94) and 0.90 (95% CrI: 0.82-0.95), respectively. The estimates of capacity spared of highest relevance to the decision problem came from diagnostic yield studies that recruited populations which matched the NICE scope. The estimates were: FIT <10µg/g: [redacted],[40] FIT10-100µg/g:[33, 40] [redacted] and 50% and post-polypectomy surveillance: [redacted][40] For patients with an incomplete COL or who refused COL, studies with mixed populations reported that, subsequent to CCE, the proportion of patients who were referred for subsequent procedures (COL, surgery, polypectomy, CTC or other unspecified therapies) ranged from 22%[73] to 76%,[53] and specifically for COL from 26%[62] to 70%.[53] When including CCEs that completed incomplete COLs in the completion rate, it ranged from 70%[58] to 98%.[62] Patient preference studies showed that patients varied in their opinions. Overall, whilst there were aspects of CCE that patients liked, such as the freedom to carry on with activities of daily living and the lower levels of pain and discomfort associated with the test in comparison to COL, there were some patients who were dissatisfied with the test due to discomfort and inconvenience from wearing the belt and recorder and due to pain, discomfort and inconvenience associated with swallowing the pill and the bowel preparation regimen, which may be more intensive than that for COL. Overall, CTC was generally preferred over CCE, and there was evidence that COL may still be preferred by patients in some clinical situations. Aspects that could be improved included the bowel preparation regimen and patient information leaflets.

5.1.2 Cost-effectiveness – principal findings

For COL-eligible patients within all three main analysis populations, the EAG's model suggests that CCE is expected to lead to small QALY losses and incur higher costs than COL; therefore, CCE is expected to be dominated by COL. The main reasons underpinning this finding are: (i) COL is assumed to have higher sensitivity than CCE for detecting polyps and CRC which leads to slightly fewer QALYs for CCE; (ii) a large proportion of CCEs are incomplete and these patients are assumed to require further tests, which leads to increased costs, and (iii) patients in whom CCE detects significant bowel pathology also require COL/FSIG to enable biopsy or polypectomy, which also leads to increased costs. For COL-

ineligible patients, CCE is either expected to be dominated by CTC or it has an ICER which is markedly higher than £30,000 per QALY gained. The main reasons for this finding are: (i) CTC is assumed to have higher sensitivity than CCE for detecting AAs and CRC which leads to slightly fewer QALYs for CCE in the symptomatic FIT 10-100µg/g and surveillance populations; (ii) the cost per CTC procedure is lower than that for CCE, and (iii) a large proportion of CCEs are incomplete and these patients are assumed to require CTC as a replacement test, leading to increased costs.

However, CCE is expected to lead to substantial reductions in the number of COLs required, particularly for the COL-eligible symptomatic patients, which may help to release capacity in constrained endoscopy services.

5.2 Strengths and limitations of the assessment

5.2.1 Strengths and limitations in the clinical evidence base

The strengths and limitations of the evidence base are discussed in detail in Section 3.4. The strengths of this work are that the systematic review was conducted following a rigorous and high-quality methodology including a comprehensive search strategy, double-screening of all retrieved records, double-checking of all extracted data and a high quality statistical synthesis conducted using a Bayesian approach.

There are, however, some significant limitations to the review, mostly relating to the quantity of data available that met the decision problem outlined in the final NICE scope.[35] The EAG had to widen the inclusion criteria for the review in order to include the best available evidence in terms of rigour (methodological quality) and relevance (generalisability). Widening review criteria *post hoc* in this fashion was necessary due to the lack of available data, but leaves the review at risk of biases being introduced, such as selection bias. However, the EAG used the principles of selecting good quality, relevant data to determine how to widen the review, and applied these systematically to the evidence base. All exclusions are documented with reasons for the decisions made. The risk of introducing selection bias is likely to be low.

This widening of the criteria has led to an evidence base that covers the scope in a piecemeal fashion. Estimates of diagnostic test accuracy came from studies with unclear (potentially poor) generalisability but with fair to good methodological quality. These studies could not be used to provide prevalence estimates for underlying disease pathology for the EAG's economic model, and therefore studies in the correct population that reported diagnostic yield rather than test accuracy were included to provide some data to base these estimates on. For patients with incomplete COL or who refused COL, there were no studies in patients solely referred for reasons listed in the NICE scope, leading to the inclusion of studies with low generalisability due to having recruited mixed populations. The impact and direction of effect

of these limitations in the rigour and relevance of the evidence base, and of obtaining test accuracy and prevalence estimates from different sources, are difficult to quantify or predict.

5.2.2 Strengths and limitations relating to the health economic analysis

The EAG's economic model is subject to several strengths. Of particular note: the economic analysis is consistent with the NICE Reference Case[119] and aligns with the final NICE scope;[35] the model uses data from the NHSE CCE Pilot Study[40] to inform estimates of the prevalence of significant bowel pathology, the CCE completion rate and the use of COL/FSIG as a subsequent luminal investigation after CCE; [redacted]; long-term outcomes are informed by the MiMiC-Bowel screening model,[111, 122] and a comprehensive range of sensitivity analyses has been conducted to explore key areas of uncertainty.

Limitations of the EAG's model include: inconsistencies in the definitions of polyp risk groups between evidence sources; the need for additional assumptions to derive prevalence estimates from the NHSE CCE Pilot Study data which leads to uncertainty; uncertainty in the estimates of diagnostic test accuracy for CCE and comparators, and the exclusion of older or frail patients from the economic analyses.

5.3 Uncertainties

As discussed in Section 5.2.1, the impact and direction of effect of the limitations of the evidence base are difficult to quantify or predict. There remain uncertainties in the estimates of diagnostic test accuracy for the populations defined in the NICE scope. There is also uncertainty with respect to the true prevalence of underlying disease in these populations, since the NHSE CCE Pilot Study did not test patients who were CCE-negative to determine FNs. It is uncertain what criteria would be used to select patients for CCE in NHS practice, and therefore whether estimates from the NHSE CCE Pilot Study will be generalisable to this population. There were no data relating to patient acceptability in surveillance populations alone, and it is uncertain whether preferences may be different in this group. There were no data on whether socioeconomic characteristics or ethnicity may impact patient preference, or other outcomes in this assessment. The impact on patient preference of the risk of having to have a subsequent COL, of the comparative accuracy of the tests and of different bowel preparation regimens was not clear to the EAG.

5.4 Generalisability

The evidence on the diagnostic test accuracy of CCE included in the EAG's meta-analysis and economic model does not align well with the populations listed in the final NICE scope.[35] It is unclear whether similar estimates of diagnostic accuracy would be achieved if CCE was used in routine NHS practice.

The EAG's economic analysis does not include consideration of older or frail patients who are unable to undergo COL. However, the EAG believes that the value of CCE over CTC in these patients is likely to be limited because CCE requires more intensive bowel preparation and because it is more expensive than other tests such as CTC.

5.5 Implications for service provision

To date, CCE has been used as an alternative to COL in only a minority of NHS centres. If CCE is recommended for bowel investigations in symptomatic or surveillance patients in routine NHS practice, the following implementation-related issues will require consideration:

- Which patients might be suitable for CCE (e.g., based on their underlying level of risk and likely need for subsequent COL)?
- Which healthcare professional(s) should provide pre-assessment for CCE in order to ensure patient safety, reduce the risk of AEs and optimise completion rates?
- Where should the capsule be swallowed (e.g., at home, or in a primary or secondary care setting)?
- Which healthcare professional(s) should supervise swallowing of the capsule?
- What measures should be in place to mitigate the risks of capsule retention (e.g., use of dissolvable patency capsules and/or CT scans)?
- Which healthcare professional(s) should read and interpret the recorded capsule data?
- What measures can be implemented to improve capsule completion rates (e.g., improved bowel preparation)?

As indicated by the EAG's economic analysis, the use of CCE is expected to impact on the provision of other services through freeing up capacity for colorectal endoscopy services.

5.6 Suggested research priorities

Further research in the following areas may be valuable:

- Further studies to assess the diagnostic test accuracy of CCE in the populations listed in the NICE scope would be valuable in reducing current uncertainty. It is anticipated that the ongoing ColoCap study (NIHR158034) will provide key evidence in this area.
- Further research into the optimal setting for delivering CCE (e.g., primary care, secondary care or at home) may help to reduce service implementation costs.
- Qualitative research into patient experience may help to identify barriers and facilitators to the acceptability and uptake of CCE.
- Further research into CCE bowel preparations may help to further improve test completion rates and reduce costs.

- An evaluation of AI/machine learning alongside CCE may help to understand the impact of such technologies on the diagnostic accuracy of CCE.

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9 APPENDICES

Appendix 1: Inclusion criteria widening and mapping of available studies

Only four studies met the original inclusion criteria for the review. These included: one diagnostic test accuracy study[57] in symptomatic patients, but which only reported data for "clinically significant disease", "any positive finding" and "significant polyps", all of which had somewhat uncertain definitions, and three studies reporting patient preference outcomes in symptomatic patients, reported over 4 publications.[34, 45, 63, 71] This meant that there were insufficient data to inform the model relating to diagnostic test accuracy.

Inclusion criteria were therefore widened in accordance with the principles described in Section 3.2.1. The evidence map that was created as part of the inclusion-widening process is provided in Table 54. As a result of this mapping exercise, studies reporting data of the highest relevance (in terms of the recruited population) and/or the highest methodological quality (in terms of study design) were selected for inclusion.

For diagnostic test accuracy, since there were no studies with more than 80% of participants meeting the review criteria, two criteria were widened separately. In "Widened 1," test accuracy studies with mixed populations, at least some of whom were patients defined in the NICE scope,[35] were included. This resulted in the exclusion of studies undertaken exclusively in screening populations. Since there were also studies of diagnostic yield within populations that met the inclusion criteria (including one from England with exactly the right populations),[40] the criteria relating to the reference standard/outcome were also separately widened ("Widened 2"). Yield studies in mixed populations (i.e., widening both the population and reference standard/outcome) were not included, since these studies would have both low internal and external validity. However, this left very little data on patients with incomplete COL or people who refused COL, and in this instance, the criteria for both the population and the reference standard/outcome were widened. This is denoted in Table 54 as "Widened 3". For the population, we applied a cut-off of >50% defined in the NICE scope,[35] because there were sufficient studies that met this criterion. These studies are of a low quality and relevance overall, but are included to provide some information about patients who refused or had an incomplete COL.

For patient preference studies, it was not necessary to widen the criteria for symptomatic patients, since some studies were available that met the original criteria. However, for surveillance patients, the criteria were widened to include one study that had >50% patients in scope, some of whom were under surveillance for previous polyps ("Widened 4"). For the study that was included, it was, however, unclear how many with "previous polyps" met the criteria of "post-polypectomy surveillance COL at 3 years because of high-risk findings at their baseline COL".

In accordance with Section 3.1.2, where studies were unclear in some details, e.g., recruitment criteria, authors were contacted if the study was of high relevance or of high quality, but authors of studies which are lower down in the hierarchy of evidence were not contacted due to time constraints. Consequently, the EAG attempted to contact the corresponding authors for Ismail *et al.,* 2021,[57] Ojidu *et al.,* 2018[71] and Takashima *et al.,* 2021,[52] but in all cases, the EAG received no reply. The queries for Ojidu *et al.,* 2018[71] and Takashima *et al.,* 2021,[52] related to which capsule test was used. Since the EAG was relatively confident that PillCam COLON 2 would be the test used in the UK in that time period, we included Ojidu *et al.,* 2018,[71] but noted the uncertainty. However, since Takashima *et al.,* 2021,[52] stated that the test used was "*PillCam COLON capsule*" this study was excluded. The query for Ismail *et al.,* 2021,[57] related to the outcome definitions. The study was included, and these uncertainties were reported in Section 3.3.2.

Consequently, five groups of studies were identified and included in the review:

- Diagnostic test accuracy studies meeting the inclusion criteria (n=1)[57]
- Diagnostic test accuracy studies in mixed populations (Widen 1, n=5)[42, 46, 60, 75, 77]
- Yield studies in the correct populations (Widen 2, n=4, reported across 7 sources)[31, 33, 34, 40, 68, 78]
- Yield studies in patients with incomplete or who refused COL (Widen 3, n=7)[53, 56, 58, 62, 72, 73, 76]
- Patient preference studies in the correct population or with >50% correct population some of whom were under surveillance for previous polyps (No widening, n=3, Widen 4, n=1, reported across 5 sources)[34, 45, 63, 66, 71]

Table 54: Evidence map of studies that were of potential relevance

Criteria widened	Symptomatic or post-polypectomy 3-year surveillance populations	Incomplete or declined COL	Patient preference
Include			
None	**Ismail 2021[57]** NB: did not report DTA for polyps by size category	No studies identified	**Ismail 2022[45]** **Ojidu 2018[71] & Ojidu 2017[63]** NB: unclear if PillCam COLON 2 **Wales pilot study[34]** **Bond 2023 (ScotCap)[66]**
Widened 1: Diagnostic test accuracy studies in mixed populations			
Widen population to include studies that recruited mixed populations with at least	**Eliakim 2009[75]** **Hagel 2014[60]** **Spada 2011[77]** **Morgan 2016[42]**	**Excluded: Takashima 2021,[52]** unclear if PillCam COLON 2	No studies identified

Criteria widened	Symptomatic or post-polypectomy 3-year surveillance populations	Incomplete or declined COL	Patient preference
some scope[35]-defined patients	**Omori 2024[46]** **Excluded: Akyuz 2016[64]** (recruitment criteria not reported); **Semenov 2022[69]** (up to 2 years to reference standard; only reports all polyps)		
Widened 2: Diagnostic yield studies in correct population			
Widen outcome to include yield studies	**Turvill 2023[32, 40, 68, 78]** NHSE CCE pilot study **MacLeod 2022[31]** SCOT-CAP **Mahdi 2023**[33] (Barnsley, England) **Wales Pilot Study[34]** (unpublished)	No studies identified	No studies identified
Widened 3: Widen both population and reference standard/outcomes			
Widen population as in "Widen 2", and reference standard to include non COL or non-CTC reference standards	**Excluded** as sufficient data from studies with greater internal or external validity: **Kroijer 2019[54]**	No studies identified	**Excluded** as sufficient data from studies with greater internal and external validity **Parisi 2024[67]** Unknown indication, only 27.6% had CCE **McKenzie 2022** Only 14/231 (6%) in-scope

Criteria widened	Symptomatic or post-polypectomy 3-year surveillance populations	Incomplete or declined COL	Patient preference
Widen population as above, and reference standard/outcome to include yield studies with no FN follow-up	**Excluded** as sufficient data from studies with greater internal or external validity: **Hartmann 2012**[74] (N.B., unclear if PillCam COLON 2) **Hausmann 2021**[61] **Ohmiya 2019**[70]	**Spada 2015**[62] **Deding 2020**[58] **Benech 2021**[56] **Baltes 2018**[73] **Havshoi 2023**[53] **Hussey 2018**[76] **Negreanu 2013**[72] (unable or unwilling) **Excluded: Nogales 2017,**[79] referral criteria NR; **Otani 2020,**[65] referral criteria unclear; **Hale 2015,**[59] >50% out of scope; **Ivanova 2015,**[55] >50% out of scope; **Lima 2024,**[80 55] >50% out of scope	
Widened 4: For studies in surveillance populations, widen population to include patient preference studies with >50% patients in scope, including some patients under surveillance for previous polyps			
Widen population to include studies that recruited with 50% patients in scope, including some patients under surveillance for "previous polyps"	**N/A**	**N/A**	**Bond 2023 (ScotCap)**[66]

DTA - diagnostic test accuracy; NHSE - National Health Service England; CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FN - false-negative; N/A - not applicable

Appendix 2: Search strategies for clinical and economic systematic reviews

Search strategies for systematic review of clinical effectiveness

This appendix contains:

- 1. Search strategies for the review of clinical evidence
  - 1.1 Initial searches
  - 1.2 Additional searches
- 2. Search strategies for systematic review of existing economic evaluations.

1. Search strategies for the review of clinical evidence

1.1 Initial searches

DATABASE SEARCHES

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 08, 2024>

1	exp Colon/	76530
2	(colon* or colo* or rectum or rectal or bowel*).mp.	1574093
3	1 or 2	1574093
4	Capsule Endoscopy/	3684
5	capsule endoscop*.mp.	6241
6	(pillcam or pill-cam).mp.	297
7	CCE.mp.	1934
8	4 or 5 or 6 or 7	8003
9	exp Colorectal Neoplasms/	248212
10	(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.	5280634
11	9 or 10	5280730
12	3 and 8 and 11	1490
13	limit 12 to yr="2009 -Current"	1170

Embase <1974 to 2024 Week 31>

1	exp Colon/	105017
2	(colon* or colo* or rectum or rectal or bowel*).mp.	2251347
3	1 or 2	2254670
4	Capsule Endoscopy/ or capsule endoscope/	12456
5	capsule endoscop*.mp.	13457
6	(pillcam or pill-cam).mp.	1467

7	CCE.mp.	2375
8	4 or 5 or 6 or 7	15470
9	exp colorectal tumor/	485678
10	(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.	7152643
11	9 or 10	7154598
12	3 and 8 and 11	4446
13	limit 12 to yr="2009 -Current"	3919
14	limit 13 to conference abstract	1471
15	13 not 14	2448
16	limit 15 to "remove medline records"	835

Search Name: COCHRANE LIBRARY

Date Run: 09/08/2024 14:54:52

ID	Search	Hits
#1	MeSH descriptor: [Colon] explode all trees	2021
#2	(colon* or colo* or rectum or rectal or bowel*):ti,ab,kw	107307
#3	#1 or #2	107307
#4	MeSH descriptor: [Capsule Endoscopy] explode all trees	178
#5	(capsule endoscop*):ti,ab,kw	1057
#6	(pillcam or pill-cam):ti,ab,kw	64
#7	(CCE):ti,ab,kw	112
#8	#4 or #5 or #6 or #7	1136
#9	MeSH descriptor: [Colorectal Neoplasms] explode all trees	12790
#10	(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*):ti,ab,kw	287002
#11	#9 or #10	287002
#12	#3 and #8 and #11	137 (trials)

WHO International Clinical Trials Registry Platform (searched 9/8/24)

(colon* or colo* or rectum or rectal or bowel*) and ("capsule endoscop*" or pillcam or pill-cam) and (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*)

– 53 results

ClinicalTrials.gov (searched 9/8/24)

Various combinations of terms including those below; duplicates removed.

colon and cancer and capsule endoscopy

colon and **p**illcam

colon and pill-cam

colon and CCE (etc.)
– 39 results

CONFERENCE PROCEEDINGS

Web of Science Conference Proceedings Citation Index (searched 13/8/24)

Searches:

1: ASCO (Conference) OR ESMO (Conference) OR AACR (Conference) Editions: WOS.ISTP Timespan: 2014-01-01 to 2024-12-31 Date Run: Tue Aug 13 2024 15:28:50 GMT+0100 (British Summer Time) Results: 155091

2: DDW (Conference) OR UEGW (Conference) OR APDW (Conference) OR BSG (Conference) Editions: WOS.ISTP Timespan: 2014-01-01 to 2024-12-31 Date Run: Tue Aug 13 2024 15:31:49 GMT+0100 (British Summer Time) Results: 35464

3: #2 OR #1 Editions: WOS.ISTP Date Run: Tue Aug 13 2024 15:32:36 GMT+0100 (British Summer Time) Results: 190555

4: ((((#2 OR #1)) AND TS=((colon* or colo* or rectum or rectal or bowel*))) AND TS=(capsule endoscop* or pillcam or pill-cam or CCE)) AND TS=(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*) Editions: WOS.ISTP Date Run: Tue Aug 13 2024 15:34:55 GMT+0100 (British Summer Time)

Results: 11

Embase <1974 to 2024 Week 32> (searched 13/8/24)

1 (American Society of Clinical Oncology or ASCO or European Society for Medical Oncology or ESMO or American Association for Cancer Research or AACR or European Cancer Summit or Digestive Disease* Week or DDW or United European Gastroenterology Week or UEGW or Asian Pacific Digestive Week or APDW or British Society of Gastroenterology or BSG).nc. 361975

2 limit 1 to (conference abstract status and yr="2014 -Current") 250254

3 exp Colon/ 105105

4 (colon* or colo* or rectum or rectal or bowel*).mp. 2255280

5 3 or 4 2258610

6 Capsule Endoscopy/ or capsule endoscope/ 12466

7 capsule endoscop*.mp. 13468

8 (pillcam or pill-cam).mp. 1468

9 CCE.mp. 2377

10 6 or 7 or 8 or 9 15483

11 exp colorectal tumor/ 486737

12	(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.	7167232
13	11 or 12	7169191
14	5 and 10 and 13	4450
15	2 and 14	391
16	remove duplicates from 15	384

1.2 Additional searches

Adaptations from the initial search strategy are highlighted in bold. Searches were conducted on 24th October 2024.

MEDLINE:

1 exp Colon/

2 (colon* or colo* or rectum or rectal or bowel*).mp.

3 1 or 2

4 Capsule Endoscopy/

5 capsule endoscop*.mp.

6 (pillcam or pill-cam).mp.

7 CCE.mp.

8 4 or 5 or 6 or 7

9 capsule colonoscop*.mp. not 8

10 exp Colorectal Neoplasms/

11 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.

12 10 or 11

13 3 and **9** and 12

14 limit 13 to yr="2009 -Current"

Embase:

1 exp Colon/

2 (colon* or colo* or rectum or rectal or bowel*).mp.

3 1 or 2

4 Capsule Endoscopy/ or capsule endoscope/

5 capsule endoscop*.mp.

6 (pillcam or pill-cam).mp.

7 CCE.mp.

8 4 or 5 or 6 or 7

9 capsule colonoscop*.mp. not 8

10 exp colorectal tumor/

11 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.

12 10 or 11

13 3 and **9** and 12

14 limit 13 to yr="2009 -Current"

Cochrane:

ID Search Hits

#1 (colonoscopy not endoscopy):ti,ab,kw AND (capsule):ti,ab,kw AND (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*):ti,ab,kw (Word variations have been searched)

2. Search strategies for systematic review of existing economic evaluations

DATABASE SEARCHES

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to August 08, 2024>

1	exp Colon/	76530
2	(colon* or colo* or rectum or rectal or bowel*).mp.	1574093
3	1 or 2	1574093
4	Capsule Endoscopy/	3684
5	capsule endoscop*.mp.	6241
6	(pillcam or pill-cam).mp.	297
7	CCE.mp.	1934
8	4 or 5 or 6 or 7	8003
9	exp Colorectal Neoplasms/	248212
10	(cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp.	5280634
11	9 or 10	5280730
12	3 and 8 and 11	1490
13	limit 12 to yr="2009 -Current"	1170
14	Economics/	27539
15	exp "costs and cost analysis"/	272263
16	Economics, Dental/	1922
17	exp economics, hospital/	25938
18	Economics, Medical/	9287
19	Economics, Nursing/	4013
20	Economics, Pharmaceutical/	3144

21 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1138047
22 (expenditure$ not energy).ti,ab. 39388
23 value for money.ti,ab. 2258
24 budget$.ti,ab. 37931
25 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 1306745
26 ((energy or oxygen) adj cost).ti,ab. 4981
27 (metabolic adj cost).ti,ab. 1817
28 ((energy or oxygen) adj expenditure).ti,ab. 30406
29 26 or 27 or 28 36108
30 25 not 29 1298370
31 letter.pt. 1266191
32 editorial.pt. 701298
33 historical article.pt. 371128
34 or/31-33 2315914
35 30 not 34 1257162
36 exp animals/ not humans/ 5247134
37 35 not 36 1176672
38 13 and 37 65

Embase <1974 to 2024 Week 31> (searched 9/8/24)

1 exp Colon/ 105017
2 (colon* or colo* or rectum or rectal or bowel*).mp. 2251347
3 1 or 2 2254670
4 Capsule Endoscopy/ or capsule endoscope/ 12456
5 capsule endoscop*.mp. 13457
6 (pillcam or pill-cam).mp. 1467
7 CCE.mp. 2375
8 4 or 5 or 6 or 7 15470
9 exp colorectal tumor/ 485678
10 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp. 7152643
11 9 or 10 7154598
12 3 and 8 and 11 4446
13 limit 12 to yr="2009 -Current" 3919
14 limit 13 to conference abstract 1471
15 13 not 14 2448
16 limit 15 to "remove medline records" 835

17 Health Economics/ 36704
18 exp Economic Evaluation/ 372544
19 exp Health Care Cost/ 356615
20 pharmacoeconomics/ 13903
21 17 or 18 or 19 or 20 658895
22 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1494992
23 (expenditure$ not energy).ti,ab. 53475
24 (value adj2 money).ti,ab. 3151
25 budget$.ti,ab. 49973
26 22 or 23 or 24 or 25 1542302
27 21 or 26 1800285
28 letter.pt. 1335730
29 editorial.pt. 817707
30 note.pt. 997617
31 28 or 29 or 30 3151054
32 27 not 31 1678733
33 (metabolic adj cost).ti,ab. 1972
34 ((energy or oxygen) adj cost).ti,ab. 5264
35 ((energy or oxygen) adj expenditure).ti,ab. 39095
36 33 or 34 or 35 45070
37 32 not 36 1669557
38 animal/ 1674422
39 exp animal experiment/ 3226396
40 nonhuman/ 7823216
41 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. 6715367
42 38 or 39 or 40 or 41 10813449
43 exp human/ 26917133
44 human experiment/ 668000
45 43 or 44 26919893
46 42 not (42 and 45) 7557882
47 37 not 46 1500865
48 0959-8146.is. 68750
49 (1469-493X or 1366-5278).is. 19513
50 1756-1833.en. 45207
51 48 or 49 or 50 114951

52 47 not 51 1493847

53 conference abstract.pt. 5203813

54 52 not 53 1206238

55 13 and 54 152

Econlit <1886 to August 1, 2024> (searched 9/8/24)

1 (colon* or colo* or rectum or rectal or bowel*).mp. 18620

72 endoscop*.mp. 22

3 (pillcam or pill-cam).mp. 0

4 CCE.mp. 143

5 2 or 3 or 4 165

6 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp. 2166

7 1 and 5 and 6 4

INAHTA HTA database (searched 9/8/24)

(colon* or colo* or rectum or rectal or bowel*) AND (pillcam or pill-cam or capsule endoscop*)

FROM 2009 TO 2024

= 39 results

CONFERENCE PROCEEDINGS

Embase <1974 to 2024 Week 32>

1 (American Society of Clinical Oncology or ASCO or European Society for Medical Oncology or ESMO or American Association for Cancer Research or AACR or European Cancer Summit or Digestive Disease* Week or DDW or United European Gastroenterology Week or UEGW or Asian Pacific Digestive Week or APDW or British Society of Gastroenterology or BSG).nc. 361975

2 limit 1 to (conference abstract status and yr="2014 -Current") 250254

3 exp Colon/ 105105

4 (colon* or colo* or rectum or rectal or bowel*).mp. 2255280

5 3 or 4 2258610

6 Capsule Endoscopy/ or capsule endoscope/ 12466

7 capsule endoscop*.mp. 13468

8 (pillcam or pill-cam).mp. 1468

9 CCE.mp. 2377

10 6 or 7 or 8 or 9 15483

11 exp colorectal tumor/ 486737

12 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp. 7167232
13 11 or 12 7169191
14 5 and 10 and 13 4450
15 2 and 14 391
16 remove duplicates from 15 384
17 Health Economics/ 36715
18 exp Economic Evaluation/ 373007
19 exp Health Care Cost/ 357041
20 pharmacoeconomics/ 14246
21 17 or 18 or 19 or 20 659928
22 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. 1498260
23 (expenditure$ not energy).ti,ab. 53582
24 (value adj2 money).ti,ab. 3156
25 budget$.ti,ab. 50054
26 22 or 23 or 24 or 25 1545656
27 21 or 26 1803938
28 letter.pt. 1337556
29 editorial.pt. 818988
30 note.pt. 998684
31 28 or 29 or 30 3155228
32 27 not 31 1682275
33 (metabolic adj cost).ti,ab. 1974
34 ((energy or oxygen) adj cost).ti,ab. 5267
35 ((energy or oxygen) adj expenditure).ti,ab. 39131
36 33 or 34 or 35 45111
37 32 not 36 1673095
38 animal/ 1675219
39 exp animal experiment/ 3230586
40 nonhuman/ 7834565
41 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. 6721699
42 38 or 39 or 40 or 41 10826259
43 exp human/ 26964515
44 human experiment/ 668789
45 43 or 44 26967291
46 42 not (42 and 45) 7565334

47 37 not 46 1503969

48 0959-8146.is. 68765

49 (1469-493X or 1366-5278).is. 19513

50 1756-1833.en. 45233

51 48 or 49 or 50 114977

52 47 not 51 1496951

53 15 and 52 24

Appendix 3: Data extraction fields for the clinical SLR

Table 55: Data extraction fields for the clinical SLR

Category	Item	Details
Study details	Author, Year	
	Manuscript type	e.g. full text, abstract, correspondence/letter
	Source of funding	
	Study objective	
	Study design	Studies may involve any of the following: a) Diagnostic cohort [single gate], b) Case-control [two gate]) - EXCLUDE
	Study type	e.g. prospective or retrospective
	Recruitment method	e.g. Consecutive sampling, convenience sampling, NR
	Study period	e.g. dates from/to
	Centres	Single or multicentre (if multicentre state N)
	Country	
Inclusion/exclusion criteria		Verbatim where possible
	Exclusion criteria	Verbatim where possible
	Summary description (brief)	Brief description of included patients e.g. Patients scheduled to undergo colonoscopy for known or suspected colonic disease; Patients in the national CRC screening program with positive iFOBT for whom colonoscopy was offered; Patients in a pilot CRC screening program with at least 1 positive FOBT result
Population characteristics at baseline	Mean Age	Mean Age (±SD years)
	Median age	Median age (range)
	Gender	Female n/N (%)
	Ethnicity reported	Yes/No

Category	Item	Details
	Ethnicity breakdown	(n, %) e.g. White, Asian, Black etc
	Indications	n CRC screening
		n FIT/FOBT+
		n Imaging tests +
		n Family/ personal history
		n Symptoms
		n Polyp surveillance
		n Other
Diagnostic test and reference standard	Description of index test	(e.g. CCE-2)
	Who read the test?	e.g., nurse, clinician, both
Bowel preparation	Laxative administered	Yes/No
	Laxative type	e.g. PEG, macrogol, novuprep
	Laxative volume administered	(L)
	Booster (e.g Sodium Phosphate [NaP]; sodium picosulfate [SPS] etc)	(e.g Sodium Phosphate [NaP]; sodium picosulfate [SPS] etc)
	Booster volume administered	(L)
	Suppository after booster	Yes/No
	Suppository dose	e.g., mg
Outcome: Bowel cleansing level	Adequate cleansing level	(%)
Outcome: Capsule completion rate	Excretion rate <8h (%)	
	Excretion rate 8-10h (%)	
	Excretion rate >10h (%)	
	Colon transit time (mean / median minutes)	
	Completion rate (excretion of capsule in battery life with complete visualisation of the colon)	
Outcome: Uptake	Uptake of PillCam COLON 2	Test accuracy studies unlikely to report this outcome; can't tell if people refused CCE because of other aspects of study, e.g., having to have two tests
Reference standard	Description of reference standard	e.g., Colonoscopy, CT Colonography, other (describe)
	Definition of target condition	e.g., Colon cancer and types
	Reference timing	e.g., Timing of colonoscopy (same day as CCE vs. different)
	Reference standard blinding to CCE-2	e.g., Yes/No, brief description
	Follow-up period	
Number of patients	Total no. of patients included (Recruited)	n
	Number of patients not followed (lost to follow up)	n

Category	Item	Details
	Reasons for withdrawal (brief)	n with reason
	Number of patients analysed	n
Outcomes: Diagnostic Accuracy	Per patient or per polyp?	Were data reported per patient, or per polyp?
	CCE size	In mm
	COL target	In mm
	Prevalence of endpoint	(TP +FN) / (TP+FP+FN+TN)
	True Positive (TP)	n
	False Positive (FP)	n
	False negative (FN)	n
	True negative (TN)	n
	Total (N)	n
	Number with condition (n)	Use if study only reports sensitivity/ specificity data to allow back-calculation of 2x2 table
	Calculated from 2x2 (or reported)	Sensitivity (TP/TP+FN)
		Specificity (TN/TN+FP)
	AUC, if reported	
Additional Information	Sensitivity data reported separately according to type of AAS (i.e. sensitivity for type A, sensitivity for type B etc)?	Yes / No (can extract later if needed)
	Results of second colonoscopy, re-read of test or polyps in different size categories	
	Yield data for CCE, COL, CTC	Only use if not calculable from TP+FP
Other Outcomes in NICE scope	Detection rates with CCE, colonoscopy or CTC for: polyps (including adenomas); cancer; other bowel pathology	
	Reduction in number of colonoscopies/number of colonoscopies potentially prevented (diagnostic, therapeutic, urgent and non-urgent)	

Category	Item	Details
	Proportion of people requiring follow up colonoscopy or other investigations such as flexible sigmoidoscopy after CCE/colonoscopy and CTC (diagnostic, therapeutic, urgent, non-urgent)	
	Number of polyps missed (including high-risk, intermediate risk and low risk polyps)	
	Numbers of cancers missed	
Clinical Outcome	Number of colorectal cancer diagnoses	
	Stage of detected cancers	
	Number/ proportion of people identified with other bowel pathologies	
	Number/proportion of people with advanced adenomas detected or detected and treated	
	Mortality	
Outcomes: patient-reported	Health related quality of life	
	Anxiety associated with waiting for procedures or test results because of diagnostic delays, and further diagnostic workup	
	Preference for CCE versus colonoscopy or CT colonography	
Adverse events	total in analysis	Number of patients in the analysis
	AE's related to bowel preparation	n
	Difficulty in swallowing capsule	n
	Capsule retentions	n
	Technical failure	n
	Colonoscopy AEs	n
Comments	Comments	Any information about the study of importance not already captured

Appendix 4: Risk of bias assessment for the diagnostic test accuracy studies

This section includes:

- The scoring criteria for the risk of bias assessment (Table 56)
- The risk of bias scores for diagnostic test accuracy studies, with reasons for scores (Table 57)
- The risk of bias scores for patient preference studies, with reasons for scores (Table 58)

Table 56: Scoring criteria for QUADAS 2[43] assessment

DOMAIN 1: PATIENT SELECTION **Section A: Risk of bias**	**1. Was a consecutive or random sample of patients enrolled?** o Score yes if states consecutive or random o Score no if states another method of patient sampling/selection o Score unclear if ambiguous
	2.Was a case-control design avoided? o Score yes if not case control o Score no if case control o Score unclear if unclear
	3. Did the study avoid inappropriate exclusions? We are interested in studies that select either • Adults with lower gastrointestinal signs or symptoms suggestive of colorectal cancer who are referred to secondary care • Adults who are due to have a post-polypectomy surveillance colonoscopy at 3-years because of high-risk findings at their baseline colonoscopy o Score yes if the study has appropriately selected patients o Score no if the study has made inappropriate exclusions from the group it set out to select e.g. excluded patients who are harder or easier to diagnose, excluded based on age or other characteristics that may affect the accuracy of the test o Score unclear if it is unclear
SUMMARY of DOMAIN 1, SECTION A:	**Could the selection of patients have introduced bias?** Low/High/Unclear THIS IS A SUMMARY SCORE BASED ON ANSWERS TO QUESTIONS 1 TO 3. Score Low if all domains are Yes Score High if one or more domain is No Anything in between score Unclear

DOMAIN 1, SECTION B: Concerns regarding applicability **Do patients in the trial represent the cohort of interest exclusively and in its entirety?**	**1. Is there concern that the included patients and settings do not match the review question?** Low/High/Unclear Rated "Low (concerns)" if study includes only patients with signs or symptoms suggestive of colorectal cancer (CRC); or due to have post-polypectomy surveillance colonoscopy at 3-years , "High" if patients are not representative of patients with signs/symptoms of CRC etc and "unclear" if not well described
DOMAIN 2: INDEX TESTS **SECTION A: risk of bias**	**1. Were the index test results interpreted without knowledge of the results of the reference standard?** o Score yes if index test was interpreted blind to the reference standard or the index test was clearly interpreted before the reference standard was known. o Score no if results of reference standard were already known o Score unclear if ambiguous
	2. If a threshold was used, was it pre-specified? o Score yes if thresholds/cut ofF values of the index test were pre-specified (validation study) o Score no if thresholds/cut-off values were fitted to the data or not pre-specified (derivation study) or o Score unclear if ambiguous
SUMMARY DOMAIN 2, SECTION A	**Could the conduct or interpretation of the index test have introduced bias?** Low/High/Unclear **THIS IS A SUMMARY SCORE BASED ON ANSWERS TO QUESTIONS 1 TO 2.** Score Low if all domains are Yes Score High if one or more domain is No Anything in between score Unclear

DOMAIN 2, SECTION B: concerns regarding applicability	**1. Is there concern that the index test, its conduct, or interpretation differ from the review question?** Low/High/Unclear Variations in test technology, execution, or interpretation may affect estimates of its diagnostic accuracy. If index tests methods vary from those specified in the review question there may be concerns regarding applicability. Since no details were specified in the scope about bowel preparation, any bowel preparation method is acceptable. The system consists of 3 components: the capsule, recorder with sensors, and desktop software. Deviation from proprietary software may score "high" - please add note about software deviation. Scope states that readings may be done by clinician or nurse practitioner, so both are acceptable personnel Scope states that CCE can be done in primary care and community settings under the supervision of secondary care. Swallowing of the pill should be supervised by clinical staff at the least, regardless of the setting for the remainder of the test. Target condition should be as defined in the scope (polyps <6mm, 6-9mm, ≥10mm), but other outcomes such as "significant polyps" may be reported - do not consider this a risk of bias, but note the outcome definition.
DOMAIN 3: REFERENCE STANDARD **SECTION A: risk of bias**	**1. Is the reference standard likely to correctly classify the target condition?** o Score yes if the reference standard is colonoscopy or CTC for all patients o Score no if the reference standard is not colonoscopy or CTC for all patients o Score unclear if ambiguous
	2. Were the reference standard results interpreted without knowledge of the results of the index test? o Score yes if the reference standard was interpreted blind to the index test or the reference standard was clearly interpreted before the index test was known. o Score no if the results of the index test were known. o Score unclear if unclear
SUMMARY DOMAIN 3, SECTION A	**Could the reference standard, its conduct, or its interpretation have introduced bias?** Low/High/Unclear (THIS IS A SUMMARY SCORE BASED ON ANSWERS TO QUESTIONS 1 TO 2)
DOMAIN 3, SECTION B concerns regarding applicability	**Is there concern that the target condition as defined by the reference standard does not match the review question?** **Low/High/Unclear**

DOMAIN 4: FLOW AND TIMING **SECTION A: risk of bias**	**1. Was there an appropriate interval between index test(s) and reference standard?** o Score yes if conducted within 6 months o Score no if conducted more than 6 months apart o Score unclear if unclear
	2. Did all patients receive a reference standard? o Score yes if all participants who received the index test were verified using the reference standard test o Score no if some of the participants who received the index test did not receive the reference standard test (partially verified). If some participants did not receive the reference test, how many did not (of the total) o Score unclear if insufficient information is provided
	3. Did patients receive the same reference standard? o Score yes if the same reference test was used regardless of the index test results o Score no if different reference tests are used depending on results of the index tests. If different reference tests are used, what were the reasons and how many participants were involved o Score unclear if insufficient information is provided
	4. Were all patients included in the analysis? o Score yes if all patients who were recruited/enrolled into the study were included in the analysis or if sufficient explanation is provided for any discrepancy, and the reasons given would indicate patients are missing at random and of small enough numbers not to affect sensitivity/specificity o Score no if there are participants excluded from the analysis and no/insufficient explanation is given for any discrepancy o Score unclear if insufficient information is given to assess whether any patients were excluded from the analysis.
SUMMARY DOMAIN 4, SECTION A	**Summary of Q 1 to 4:** **Could the patient flow have introduced bias?** Low/High/Unclear (THIS IS A SUMMARY SCORE BASED ON ANSWERS TO QUESTIONS 1 TO 4) Score Low if all domains are Yes Score High if one or more domain is No Anything in between score Unclear

Table 57: Risk of bias scores for diagnostic test accuracy studies, with reasons for scores, as judged by the EAG

Section	Signalling question	Scope-defined populations	Mixed populations				
		Ismail 2021[57]	**Eliakim 2009[75]**	**Spada 2011[77]**	**Hagel 2014[60]**	**Morgan 2016[42]**	**Omori 2024[46]**
Domain 1 **Patient selection**							
A: Risk of bias	1. Was a consecutive or random sample of patients enrolled?	Unclear	Unclear	No – states in the abstract that sample is non-consecutive	Unclear	Unclear	Unclear
	2.Was a case-control design avoided?	Yes	Yes -	Yes	Yes	Yes	Yes
	3. Did the study avoid inappropriate exclusions?	Yes	No – excluded age over 57 years	Yes	Yes	Yes	Yes
Summary 1A	Could the selection of patients have introduced bias?	Unclear	High	High	Unclear	Unclear	Unclear
B: Concerns regarding applicability Do patients in the trial represent the cohort of interest exclusively and in its entirety?	1. Is there concern that the included patients and settings do not match the review question?	**Symptomatic population:** Unclear - referral criteria from primary care unclear **Surveillance population:** N/A	**Symptomatic and surveillance:** High - not all were a population of interest	**Symptomatic and surveillance:** High - not all were a population of interest	**Symptomatic and surveillance:** High - not all were a population of interest	**Symptomatic and surveillance:** High - not all were a population of interest	**Symptomatic and surveillance :** High- not all were a population of interest; no post-polypectomy patients

Domain 2 **Index tests**							
A: Risk of bias	1. Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	2. If a threshold was used, was it pre-specified?	NA	NA	NA	NA	NA	NA
Summary 2A	Could the conduct or interpretation of the index test have introduced bias?	Low	Low	Low	Low	Low	Low
B: Concerns regarding applicability	1. Is there concern that the index test, its conduct, or interpretation differ from the review question?	Low	Low	Low	Low	Low	Low
Domain 3 **Reference standard**							
A: Risk of bias	1. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes
	2. Were the reference standard results interpreted without knowledge of the results of the index test?	No - COL results not blinded to the result of CCE	Yes	Yes	Yes - although clinicians were unblinded in the case of a CCE finding not noted on COL, the	Yes	Yes

					results reported related to the unblinded finding		
Summary 3A	Could the reference standard, its conduct, or its interpretation have introduced bias?	High	Low	Low	Low	Low	Low
B: Concerns regarding applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low	Low	Low	Low	Low	Low
Domain 4 **Flow and timing**							
A: Risk of bias	1. Was there an appropriate interval between index test(s) and reference standard?	Unclear – scheduled "on average 4 weeks after their CCE"	Yes – within 10 hours	Yes – within 12 hours	Yes - next day	Yes - same day	Yes - within 4 months
	2. Did all patients receive a reference standard?	Yes	Yes	Yes	Yes	Yes	Yes
	3. Did patients receive the same reference standard?	Yes	Yes	Yes	Yes	Yes*	Yes
	4. Were all patients included in the analysis?	Yes – 11/77 (14.3%) excluded from analysis, but reasons for exclusion were clearly reported and unlikely to be	Yes – 6/104 (6%) patients were excluded from the analysis. Reasons for exclusion were clearly reported and unlikely to be	Yes – 8/117 (7%) patients were excluded from the analysis. Reasons for exclusion were clearly reported	Yes – 1/24 (4%) patient with incomplete CCE during capsule working time (stayed in stomach) excluded from the	Yes	No – 2/91 (2%) patients with ≥30 polyps excluded from analysis – could not

		associated with DTA	associated with DTA.	and unlikely to be associated with DTA	analysis, but small number		ensure consistency with CCE findings
Summary 4A	Summary of Q 1 to 4:	Unclear	Low	Low	Low	Low	High

CCE, colon capsule endoscopy; COL, colonoscopy; DTA, diagnostic test accuracy; NA, Not applicable.
** NB one patient received two COLs, but we were able to exclude this data from the TPs etc*

Table 58: Risk of bias scores for patient preference studies, with reasons for scores, as judged by the EAG

Category of study design	Criteria	Ismail 2022[44]		Ojidu 2018[70]		Wales pilot study[34]		Bond 2023[65]	
		Response	Description	Response	Description	Response	Description	Response	Description
All studies	**S1**	Y	-	Y	-	Y	-	Y	-
	S2	Y	-	Y	-	Y	-	Y	-
1. Qualitative*	**1.1**					?	Patient and staff experience surveys - no further details provided	Y	Service evaluation of patient acceptance and experience of colon capsule endoscopy and new care pathway introduced

	1.2					?	Unclear	Y	Paper-based survey and semi-structured interviews
	1.3					?	Unclear	Y	Thematic coding analysis and mapped to NASSS (nonadoption, abandonment, scale-up, spread, and sustainability) framework
	1.4					?	Unclear	Y	Interpretation adequately supported by data
	1.5					?	Unclear	Y	Clear links between data sources, collection, analysis and interpretation
2. Quantitative randomised control trials†	**2.1**								
	2.2								
	2.3								
	2.4								

	2.5								
3. Quantitative non-randomised‡	**3.1**								
	3.2								
	3.3								
	3.4								
	3.5								
4. Quantitative descriptive§	**4.1**	Y	All patients who had both tests within 12 months were recruited	Y	Consecutive sampling (from selected hospitals)			N	Survey: Non-probabilistic sampling (voluntary) Interview: Non-probabilistic sampling (opportunistic)
	4.2	Y	Symptomatic patients - all in scope and all who were eligible participated	Y	Symptomatic patients - all in scope			?	(1) Symptomatic patients - all in scope but referral criteria in Scotland differ from England. Unclear how different patient spectrum is to target population (2) Surveillance patients - not all in scope
	4.3	Y	10-point Likert scale, Modified-Gloucester-Comfort-Scale, other	Y	Patients: Gloucester Comfort Score (also completed by Endoscopists), Visual Analogue Scale, Friends and Family Test.			?	Unclear if survey questionnaires pre-tested prior to data collection

					Informed lay members of public: interview (approached outside a shopping centre)				
	4.4	Y	Complete participant inclusion and a 100% response rate	Y	Less than 5% of patients declined to participate in both study parts - no further details provided			?	Unclear - 211/317 (66.6%) completed survey but reported demographic data, albeit very limited, only available for 183/211 (86.7%) patients. No further details provided or analysis between responders/non-responders
	4.5	Y	Statistical analysis appropriate	Y	Statistical analysis appropriate			?	Unclear - limited details provided; no statistical analysis reported

5. Mixed methods	**5.1**							Y	Builds on quantitative (survey) findings with qualitative (interview) results to directly inform the future design of both the technology and the service delivery model in Scotland
	5.2							Y	Qualitative and quantitative components adequately integrated during the data collection analysis and interpretation
	5.3							Y	Outputs of the integration of qualitative and quantitative components adequately interpreted
	5.4							Y	Divergences and inconsistencies between quantitative and qualitative results adequately addressed

	5.5							N	Overall rating considered as low quality (quantitative component rated as low and qualitative component as high [overall quality of a mixed methods study cannot exceed the quality of its weakest component])

Y, Yes; N, No; ?, Unclear/can't tell

Screening questions (for all types) S1. Are there clear research questions? S2. Do the collected data allow to address the research questions?

* 1. Qualitative. 1.1. Is the qualitative approach appropriate to answer the research question? 1.2. Are the qualitative data collection methods adequate to address the research question? 1.3. Are the findings adequately derived from the data? 1.4. Is the interpretation of results sufficiently substantiated by data? 1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?

† 2. Quantitative randomised controlled trials. 2.1. Is randomization appropriately performed? 2.2. Are the groups comparable at baseline? 2.3. Are there complete outcome data? 2.4. Are outcome assessors blinded to the intervention provided? 2.5 Did the participants adhere to the assigned intervention?

‡ 3. Quantitative non-randomised. 3.1. Are the participants representative of the target population? 3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)? 3.3. Are there complete outcome data? 3.4. Are the confounders accounted for in the design and analysis? 3.5. During the study period, is the intervention administered (or exposure occurred) as intended?

§ 4. Quantitative descriptive. 4.1. Is the sampling strategy relevant to address the research question? 4.2. Is the sample representative of the target population? 4.3. Are the measurements appropriate? 4.4. Is the risk of nonresponse bias low? 4.5. Is the statistical analysis appropriate to answer the research question?

‖ 5. Mixed methods. 5.1. Is there an adequate rationale for using a mixed methods design to address the research question? 5.2. Are the different components of the study effectively integrated to answer the research question? 5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? 5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? 5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Appendix 5: Records excluded from the clinical SLR at full-text with reasons

Table 59 lists the records excluded from the review after consideration of their full text. It includes records from across the searches of "databases and registers" and "other sources" listed in the PRISMA flow diagram (see Figure 4). In total, 144 records were excluded after consultation of the full text; 139 from the database searches, and 5 from the other sources searches.

Table 59: Records excluded from the review with reasons for exclusions

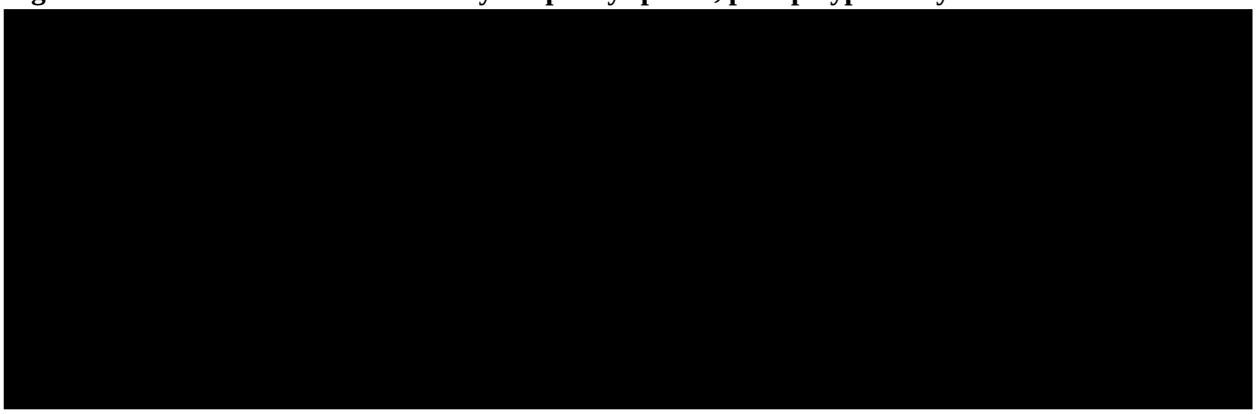
Main reason for exclusion	Additional detail	Number of studies	References
Review	Systematic review	20	58, 100-103, 105, 157-170
	Non-systematic review	8	28, 155, 171-176
Conference abstract superseded by journal article		5	177-181
Non-English language		4	182-185
Outcome/no relevant data		7	186-192
Population	Various reasons	30	55, 59, 61, 64, 65, 67, 79, 80, 84, 193-213
	Potential patient recruitment crossover with an included study	1	214
	Screening population	10	215-224
Publication type	e.g., letter to editor, editorial, protocol of published study	12	225-236
Reference standard	e.g., not colonoscopy or CTC, not conducted within 6 months of index CCE	4	54, 97, 99, 237
Study design	Case series, risk factor analysis, economic analysis	4	238-241
Test	e.g., cannot tell if Pillcam COLON 2, different brand of capsule endoscopy (e.g., OMOM), different type of capsule (e.g., small bowel or Crohn's disease capsule), Pillcam COLON (i.e., previous version of Pillcam)	42	52, 69, 70, 74, 242-279

Appendix 6: NHSE CCE Pilot Study, capacity spared estimates provided by NHSE CCE Pilot Study Investigators

Figure 12: NHSE CCE Pilot Study - capacity spared, FIT10-100µg/g

Figure 13: NHSE CCE Pilot Study - capacity spared, FIT<10µg/g

Figure 14: NHSE CCE Pilot Study - capacity spared, post-polypectomy surveillance



Appendix 7: Model estimation of the impact of delayed diagnosis of colorectal cancer and advanced adenomas on long-term outcomes and costs

1. Introduction

Diagnostic pathways for CRC (such as the former 2WW standard, which has since been replaced by the FDS, and the use of FIT testing within primary care) are important as they facilitate the early diagnosis and treatment of cancer which is important for improving survival rates. Reducing the length of time from the onset of cancer symptoms to presentation in primary care, receiving a diagnosis and starting treatment, may reduce the risk of disease progression. As CRC symptoms such as abdominal pain, rectal bleeding, change in bowel habit, and weight loss are non-specific, optimising diagnostic pathways to reduce the diagnostic interval within a service with capacity constraints is challenging.[280] Adenomas are generally asymptomatic but can be diagnosed incidentally during investigations for suspected CRC and are clinically important because adenomas (particularly AAs) have the potential to develop into CRC.[10]

The health economic evaluation of cancer diagnostic pathways requires the quantification of: (1) resource use (such as numbers and costs of diagnostic procedures undertaken), and (2) the impact of reducing/increasing the diagnostic interval for persons with underlying disease (e.g., delayed diagnosis for persons receiving an FN test result).

Existing evidence on the association between the time to diagnosis and CRC outcomes is heterogeneous. A previous systematic review explored the association between shorter times to diagnosis and more favourable outcome and found that although many studies reported no associations, more studies reported a positive, rather than a negative, association.[281]

This study involved the development of a state transition model to quantify the impact of delayed diagnosis for CRC and high-risk adenomas (HRAs) on lifetime survival, QALYs and costs from an NHS and PSS perspective. This simple model utilises outputs from an existing CRC microsimulation model (MiMiC-Bowel).[111] The estimates reported here provide key inputs for the evaluation of new diagnostic technologies or changes to existing CRC diagnostic pathways.

2. Methods

2.1 Model perspective

The model adopted a lifetime horizon to evaluate the long-term impact of delayed diagnosis on costs and health outcomes for CRC and HRAs. A discount rate of 3.5% was used to account for time preferences, in line with the NICE Reference Case.[119] The analysis was conducted from the perspective of the UK NHS and PSS, which included all costs and patient benefits associated with health care

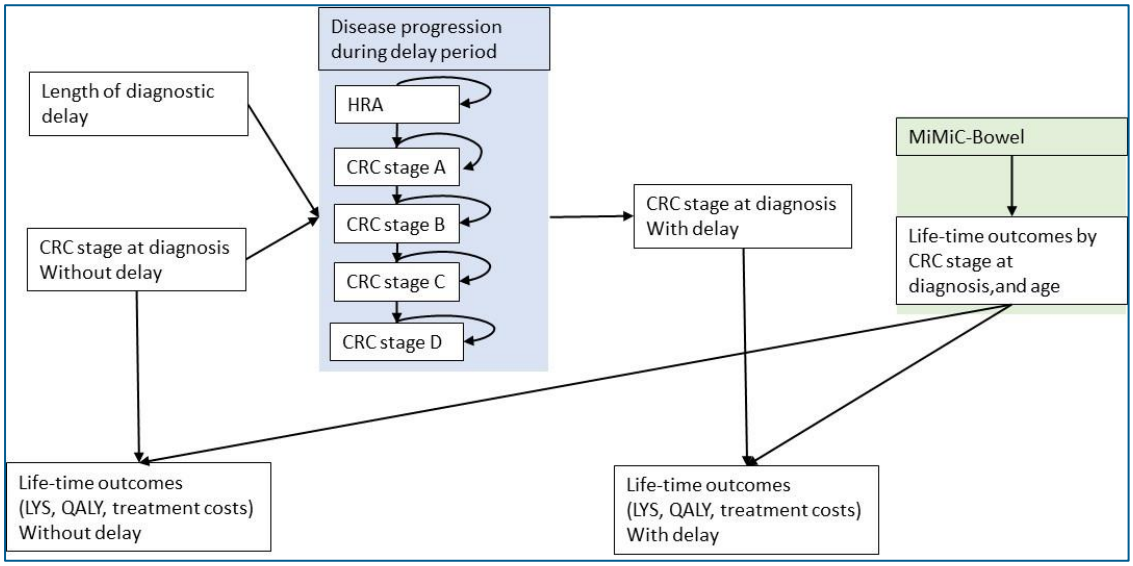
services and social care interventions. Direct costs associated with CRC diagnosis and treatment, including the costs of diagnostic tests, health care contacts, hospitalisations, medications, and palliative care, were considered. Health outcomes were measured in terms of LYs gained (or lost), and QALYs.

2.2 Model structure

A model was used to estimate the impact of a delayed diagnosis on patient outcomes. The current time to diagnosis is assumed to be the average time to diagnosis based on the most recent data available for the previous 2WW pathway. A delayed diagnosis with delay length zero reflects this average current time to diagnosis and results for delay periods >0 are compared incrementally against this.

The model structure is illustrated in Figure 15. For patients with CRC, the impact of delayed diagnosis is estimated by comparing the stage distribution of CRC at diagnosis without additional delay to the expected stage distribution of CRC at diagnosis with the additional delay. The change in stage distribution during the delayed diagnosis represents disease progression during this time period. For patients with HRAs, disease progression is represented by the proportion of individuals who develop CRC during the delayed diagnosis. These estimates of disease progression during the delayed diagnosis are combined with estimates of the differential health outcomes and costs by disease stage to produce an overall estimate of the impact of delayed diagnosis over a range of delay intervals.

Figure 15: Model structure and estimation of outcomes



CRC - colorectal cancer; HRA - high-risk adenoma; LY - life year; QALY - quality-adjusted life year

2.3 Population

The model population reflects patients referred under the 2WW system for suspected CRC in England[282] (subsequently replaced by the FDS in 2023). All individuals in the model have either CRC or HRAs. The age distributions applied for symptomatic patients with underlying disease (either CRC or HRAs) are shown in Table 60, based on data from the NCRAS.

The CRC stage distribution for the average current time to diagnosis was assumed to be the stage distribution of CRC in the 2WW population in England: 19.6%; 25.4%; 31.2%, 23.8% for Dukes' stages A-D, respectively.[124] This corresponds to patients diagnosed via symptomatic or chance detection (i.e., not via screening or surveillance). The model assumes that chance detection and symptomatic presentation are associated with the same stage distribution at diagnosis.

Table 60: Age distribution assumed for persons with CRC or HRA diagnosed via 2WW referral

Age category (years)	CRC diagnosed via 2WW		HRA diagnosed age distribution		Prevalence of CRC in 2WW referrals population
	Frequency, N	%	Frequency, N	%	
30-49	734	5%	49,251	13%	1.5%
50-59	1,814	13%	63,396	17%	2.9%
60-69	2,841	21%	85,690	23%	3.3%
70-79	4,274	32%	104,062	28%	4.1%
80-89	3,789	28%	73,564	20%	5.2%
All persons	13,452	100%	375,963	100%	3.6%

CRC - colorectal cancer; HRA - high-risk adenoma; 2WW - 2-Week Wait

2.4 Modelling disease progression during delay period

Patients enter the model in one of five health states: HRA or CRC stage A, B, C or D. During the delay period, a proportion of patients will experience a stage shift. For undiagnosed HRAs, a proportion of patients will develop CRC stage A, and for CRC a proportion of patients will advance to the next stage. The probability of transitioning depends on the length of time over which diagnosis is delayed. The transition probabilities were taken from the existing MiMiC-Bowel model,[111] as detailed in Table 61. MiMiC-Bowel reports annual transition probabilities. In this model, it was necessary to convert the reported transition probabilities into rates to estimate transition probabilities for shorter periods of time.

The model assumes that individuals can only make one state transition during each 1-year period. This assumption is consistent with the assumptions made in MiMiC-Bowel. For predictions relating to delays of >1-year, multiple transitions are included. It is assumed that all patients survive the delay period, i.e., there is no transition to "dead" in the model. This is a simplifying assumption, but is not expected to have a significant impact on the results given the short length of the delay period.

In MiMiC-Bowel, the preclinical patient population includes both asymptomatic and symptomatic patients; hence, the preclinical disease progression probabilities therefore relate to both asymptomatic and symptomatic individuals. It is plausible that a wholly symptomatic population may experience faster disease progression; this is a minor limitation of the analysis presented here.

Table 61: Disease progression transition probabilities

Transition	Transition probability (1 year) from MiMiC-Bowel	Transition rate (1-year)†
CRC A → CRC B	0.293	0.347
CRC B → CRC C	0.554	0.807
CRC C → CRC D	0.350	0.431
HRA → CRC A*	0.027	0.028

CRC - colorectal cancer; HRA - high risk adenomas
**Within MiMiC-Bowel the risk of progression is age dependent for HRA ->CRC. In this model, an average transition rate for age of 62 was applied for simplicity based on the midpoint average rate for ages 57 and 67.*
†Rates were calculated using the formula: rate, r=-ln [1-annual_trans_prob], then to estimate the transition probabilities relating to shorter time period the formula $p(t) = 1 - e^{-rt}$, where r is the rate and t is the time period was used. We note that this conversion formula has weaknesses and is most reliable for a model in which a person can experience only one type of event in a single cycle.[283]

2.5 Lifetime outcomes without a diagnostic delay for CRC

Lifetime outcomes for CRC without delayed diagnosis were estimated by undertaking new analyses using the existing MiMiC-Bowel simulation model.[111] The model was set up to best reflect current practice in CRC screening and diagnosis, i.e., individuals in the model were eligible for screening by FIT at the age of 56 years (note: the minimum age for screening eligibility was reduced to 50 years in January 2025). MiMiC-Bowel records diagnoses and outcomes separately for individuals diagnosed via screening or via symptomatic presentation. Only outcomes for individuals diagnosed symptomatically were used, as this best represents individuals in the NHS 2WW pathway.

MiMiC-Bowel was run for a population of 169,975 individuals based on 25 loops of the Health Survey for England (HSE) population. For each individual diagnosed via symptomatic/chance presentation in the model, the LYs, QALYs, and health care costs from the point of diagnosis until death were recorded. Aggregated outcomes were then subdivided according to the age group and stage at diagnosis, and the mean outcomes per age and stage at diagnosis were calculated. Details on how these outcomes are estimated by MiMiC-Bowel are reported in full in the relevant published model documentation.[111] As the costs in MiMiC-Bowel correspond to 2018 prices, aggregate costs were uplifted to 2023 values using the NHS Cost Inflation Index (NHSCII).[121]

2.6 Lifetime outcomes without a diagnostic delay for HRAs

It was implicitly assumed that individuals diagnosed with HRAs have these removed via polypectomy. It is possible that individuals with HRAs removed via polypectomy might have slightly poorer health outcomes and higher costs than the general population. This modelling exercise made a simplifying assumption that lifetime outcomes for individuals with HRAs which are removed via polypectomy would be the same as for the general population. Life expectancy for the general population was taken

from ONS life tables for England (2017-2019)[284] and age- and sex-adjusted HRQoL was based on EQ-5D-3L estimates from Hernández Alava *et al.*[126]

2.7 Lifetime outcomes with a diagnostic delay

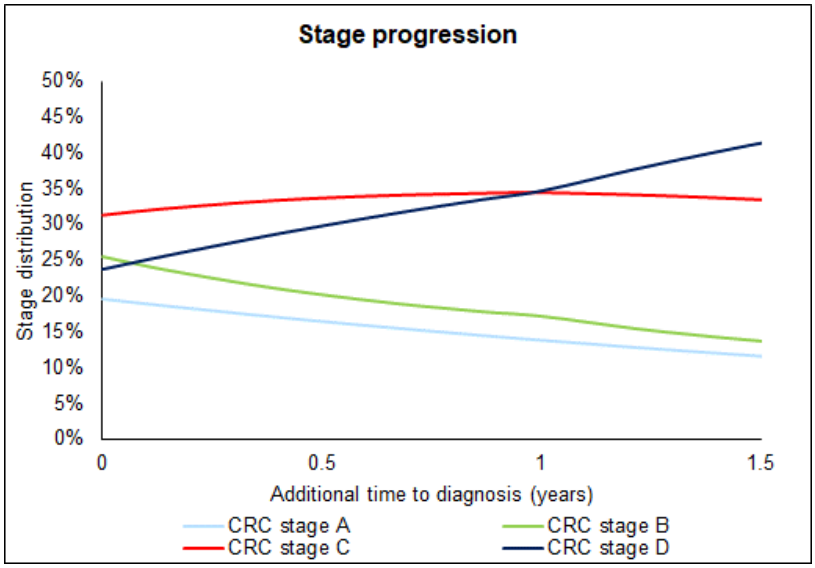
The two interim sets of results: (1) disease stage with delay, and (2) lifetime outcomes by disease state, were combined to provide an estimate of lifetime outcome for different lengths of diagnostic delay (up to 2 years). Estimates for different age groups were generated and these were combined to produce estimates which were specific to a 2WW population cohort. In addition, results for the 60-69 years age group are presented as these data were used to inform the economic analysis of CCE (Section 4.3 of this report).

3. Results

3.1 Interim results: Model estimates of disease progression

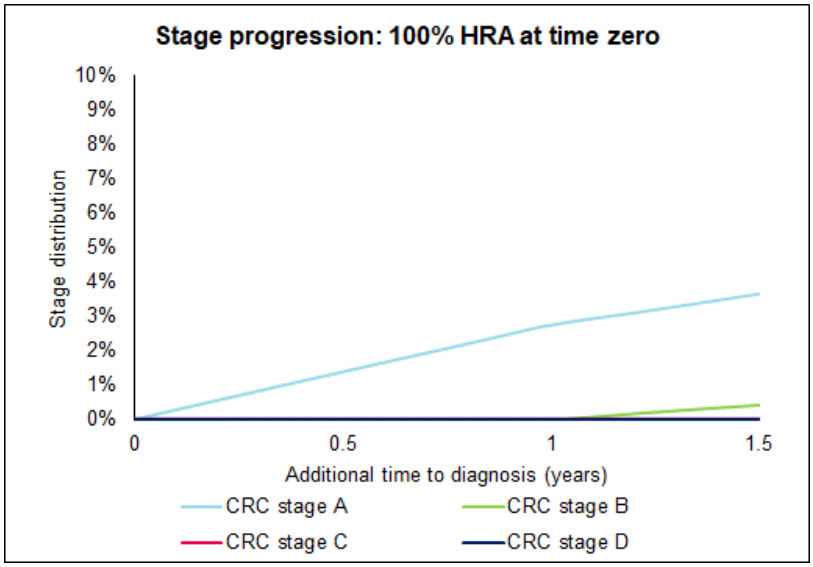
Figure 16 and Figure 17 show the impact of disease progression during the diagnostic delay period on underlying disease state which is estimated by the Markov component of the model. For CRC, it can be seen that with a longer diagnostic delay more individuals progress to late-stage CRC (stage C and D) and fewer are diagnosed in early stages (stages A and B). For HRA with a longer diagnostic delay, more individuals develop CRC.

Figure 16: Change in CRC stage distribution by duration of diagnostic delay



CRC - colorectal cancer

Figure 17: Development of CRC in a population with HRAs by duration of diagnostic delay



CRC - colorectal cancer; HRA - high-risk adenoma

3.2 Interim results: Costs and health outcomes by age and disease stage

Table 62 shows expected lifetime outcomes by age group and underlying disease state generated by undertaking re-analyses using MiMiC-Bowel. These results suggest lower expected LYs and QALYs for older age groups and more advanced stages of disease.

Fewer lifetime QALYs are accrued by individuals with CRC than with HRAs, and within CRC, fewer QALYs are accrued by individuals diagnosed at later stages than at early stages. Within each stage, individuals in older age groups accrue fewer lifetime QALYs than those diagnosed in younger age groups. Expected QALY estimates are lower than the corresponding LY estimates for people without CRC, reflecting the impact of the disease and treatment on HRQoL.

Lifetime treatment costs indicate a more complex pattern. Treatment costs for individuals with CRC are much higher than for individuals with HRA. For CRC, individuals diagnosed with stage D cancer have the lowest treatment costs (likely due to such individuals having much shorter life expectancy, and more likely to be offered only palliative treatment). The pattern across the other age groups and stages is influenced by the interactions between life expectancy and treatment options.

Table 62: Expected discounted LYs, QALYs, and inflated treatment costs by age and stage at diagnosis (excluding delay)

Age group	Expected discounted lifetime LYs					Expected discounted lifetime QALYs					Expected discounted lifetime treatment costs				
	HRA	CRC A	CRC B	CRC C	CRC D	HRA	CRC A	CRC B	CRC C	CRC D	HRA	CRC A	CRC B	CRC C	CRC D
30-49	22.05	21.74	20.00	18.89	4.02	18.58	16.91	14.65	12.94	2.80	£574	£34,191	£33,168	£44,315	£14,780
50-59	18.32	17.72	17.11	14.57	3.63	14.89	12.80	12.00	10.60	2.57	£581	£34,205	£33,410	£44,320	£14,033
60-69	14.59	14.62	13.00	11.54	2.39	11.50	9.80	9.21	8.06	2.25	£521	£34,818	£33,599	£38,324	£10,938
70-79	10.40	9.58	8.65	6.83	1.53	7.88	6.66	6.09	5.02	1.76	£385	£31,693	£30,289	£31,357	£7,438
80-89	6.30	4.98	4.49	3.50	1.28	4.53	3.67	3.53	2.93	1.54	£95	£25,306	£24,391	£24,940	£5,155

LY - life year; QALY - quality-adjusted life year; HRA - high risk adenoma; CRC - colorectal cancer

3.3 Impact of delayed diagnosis

Table 63 and Table 64 present the estimated impact of delayed diagnosis for individuals with CRC and HRAs. Table 63 presents the estimated outcomes absolute values by duration of diagnostic delay, whilst Table 64 presents incremental outcomes compared to no delay.

For CRC, a longer diagnostic delay is associated with worse health outcomes (LYs and QALYs) but lower treatment costs (due to more individuals being diagnosed in stage D which is associated with lower treatment costs).

For HRAs, a longer diagnostic delay is associated with lower expected LYs and QALYs. This reflects the disease progression to CRC in some individuals and the lower HRQoL with CRC stage A compared to HRAs. Treatment costs are higher which reflects the higher treatment costs for CRC versus HRAs.

Table 63: Estimated outcomes absolute values by duration of diagnostic delay, all ages (discounted at rate of 3.5% per year)

Additional time to diagnosis (months)	CRC expected outcomes, absolute: by time to diagnosis			HRA expected outcomes, absolute: by time to diagnosis		
	Expected discounted LYs	Expected discounted QALYs	Expected discounted lifetime treatment costs	Expected discounted LYs	Expected discounted QALYs	Expected discounted lifetime treatment costs
0.0	7.93	5.81	£26,222	13.41	10.63	£417
0.5	7.88	5.78	£26,121	13.41	10.63	£451
1	7.83	5.75	£26,020	13.41	10.63	£484
2	7.74	5.69	£25,823	13.41	10.63	£551
4	7.53	5.55	£25,353	13.41	10.62	£718
6	7.37	5.45	£24,998	13.41	10.61	£851
8	7.21	5.34	£24,621	13.40	10.61	£1,000
10	7.04	5.24	£24,228	13.40	10.60	£1,165
12	6.94	5.17	£23,968	13.40	10.59	£1,280
14	6.70	5.01	£23,350	13.39	10.58	£1,448
16	6.56	4.92	£22,962	13.39	10.58	£1,559
18	6.39	4.81	£22,505	13.38	10.57	£1,698
20	6.24	4.71	£22,076	13.38	10.56	£1,836
22	6.10	4.62	£21,674	13.38	10.55	£1,973
24	5.97	4.53	£21,297	13.37	10.55	£2,110
26	5.79	4.42	£20,800	13.36	10.54	£2,250
28	5.64	4.31	£20,335	13.36	10.53	£2,388
30	5.49	4.22	£19,899	13.35	10.52	£2,526
32	5.35	4.13	£19,491	13.35	10.51	£2,662
34	5.23	4.04	£19,110	13.34	10.50	£2,798
36	5.11	3.97	£18,753	13.33	10.49	£2,932

LY - life year; QALY - quality-adjusted life year

Table 64: Incremental outcomes (compared to no delay) by duration of diagnostic delay, all ages (discounted at rate of 3.5% per year)

Additional time to diagnosis (months)	CRC expected outcomes, incremental: by time to diagnosis			HRA expected outcomes, incremental: by time to diagnosis		
	Expected discounted LYs	Expected discounted QALYs	Expected discounted lifetime treatment costs	Expected discounted LYs	Expected discounted QALYs	Expected discounted lifetime treatment costs
0.0	0.00	0.00	£0	0.00	0.00	£0
0.5	-0.05	-0.03	-£102	0.00	0.00	£34
1	-0.10	-0.06	-£202	0.00	0.00	£67
2	-0.19	-0.12	-£399	0.00	-0.01	£134
4	-0.40	-0.26	-£869	-0.01	-0.01	£301
6	-0.56	-0.36	-£1,224	-0.01	-0.02	£434
8	-0.72	-0.47	-£1,602	-0.01	-0.03	£583
10	-0.88	-0.58	-£1,995	-0.01	-0.03	£748
12	-0.99	-0.65	-£2,254	-0.02	-0.04	£863
14	-1.22	-0.80	-£2,873	-0.02	-0.05	£1,030
16	-1.37	-0.90	-£3,260	-0.03	-0.06	£1,142
18	-1.53	-1.00	-£3,717	-0.03	-0.06	£1,280
20	-1.69	-1.11	-£4,146	-0.03	-0.07	£1,419
22	-1.83	-1.20	-£4,549	-0.04	-0.08	£1,556
24	-1.96	-1.29	-£4,926	-0.04	-0.09	£1,693
26	-2.13	-1.40	-£5,422	-0.05	-0.09	£1,833
28	-2.29	-1.50	-£5,887	-0.06	-0.10	£1,971
30	-2.44	-1.60	-£6,323	-0.06	-0.11	£2,109
32	-2.57	-1.69	-£6,731	-0.07	-0.12	£2,245
34	-2.70	-1.77	-£7,112	-0.07	-0.13	£2,381
36	-2.82	-1.85	-£7,469	-0.08	-0.14	£2,515

LY - life year; QALY - quality-adjusted life year; NMB - net monetary benefit; WTP - willingness-to-pay

Table 65: Outcomes associated with additional time to diagnosis for the 60-69 age group, for CRC

Additional time to diagnosis (months)	Absolute outcomes for 60-69 age group			Incremental outcomes for 60-69 age group		
	Expected discounted lifetime LYs	Expected discounted lifetime QALYs	Expected discounted lifetime treatment costs	Expected discounted lifetime LYs	Expected discounted lifetime QALYs	Expected discounted lifetime treatment costs
0.0	10.34	7.31	£29,919	0.00	0.00	£0
0.5	10.27	7.27	£29,812	-0.06	-0.04	-£107
1	10.21	7.23	£29,706	-0.12	-0.08	-£213
2	10.09	7.15	£29,499	-0.24	-0.16	-£420
4	9.81	6.97	£29,001	-0.52	-0.34	-£918
6	9.61	6.84	£28,624	-0.73	-0.47	-£1,295
8	9.40	6.71	£28,222	-0.94	-0.60	-£1,697
10	9.18	6.57	£27,801	-1.16	-0.74	-£2,118
12	9.04	6.48	£27,523	-1.30	-0.83	-£2,396
14	8.73	6.28	£26,855	-1.61	-1.03	-£3,063
16	8.53	6.16	£26,437	-1.80	-1.15	-£3,482
18	8.31	6.01	£25,941	-2.03	-1.30	-£3,978
20	8.10	5.88	£25,476	-2.23	-1.43	-£4,443
22	7.91	5.76	£25,039	-2.42	-1.55	-£4,880
24	7.73	5.65	£24,628	-2.60	-1.66	-£5,291
26	7.50	5.50	£24,088	-2.83	-1.81	-£5,831
28	7.29	5.36	£23,581	-3.05	-1.95	-£6,338
30	7.09	5.24	£23,106	-3.25	-2.07	-£6,813
32	6.90	5.12	£22,660	-3.43	-2.19	-£7,259
34	6.73	5.01	£22,243	-3.60	-2.30	-£7,676
36	6.57	4.91	£21,852	-3.76	-2.40	-£8,067

CRC - colorectal cancer; LY - life year; QALY - quality-adjusted life year

Table 66: Outcomes associated with additional time to diagnosis for the 60-69 age group, for HRA

Additional time to diagnosis (months)	Absolute outcomes for 60-69 age group			Incremental outcomes for 60-69 age group		
	Expected discounted lifetime LYs	Expected discounted lifetime QALYs	Expected discounted lifetime treatment costs	Expected discounted lifetime LYs	Expected discounted lifetime QALYs	Expected discounted lifetime treatment costs
0.0	14.59	11.50	£521	0.00	0.00	£0
0.5	14.59	11.49	£558	0.00	-0.00	£37
1	14.59	11.49	£595	0.00	-0.00	£73
2	14.59	11.49	£668	0.00	-0.01	£146
4	14.59	11.48	£850	0.00	-0.02	£328
6	14.59	11.47	£995	0.00	-0.02	£473
8	14.59	11.46	£1,157	0.00	-0.03	£635
10	14.59	11.46	£1,336	0.00	-0.04	£815
12	14.59	11.45	£1,461	0.00	-0.05	£940
14	14.58	11.44	£1,644	-0.00	-0.06	£1,122
16	14.58	11.43	£1,765	-0.00	-0.06	£1,244
18	14.58	11.42	£1,916	-0.01	-0.07	£1,395
20	14.58	11.42	£2,066	-0.01	-0.08	£1,545
22	14.58	11.41	£2,216	-0.01	-0.09	£1,695
24	14.57	11.40	£2,365	-0.01	-0.10	£1,844
26	14.57	11.39	£2,517	-0.02	-0.11	£1,995
28	14.56	11.38	£2,667	-0.02	-0.12	£2,146
30	14.56	11.37	£2,817	-0.03	-0.13	£2,295
32	14.55	11.36	£2,965	-0.03	-0.14	£2,444
34	14.55	11.35	£3,112	-0.04	-0.14	£2,591
36	14.55	11.34	£3,259	-0.04	-0.15	£2,737

HRA - high-risk adenoma; LY - life year; QALY - quality-adjusted life year

Appendix 8: Polyp sensitivity and specificity by size threshold/interval for CTC and colonoscopy from published meta-analyses

Table 67: Estimates of polyp sensitivity and specificity by size threshold/interval for CTC and colonoscopy from previous meta-analyses

Author	Reference standard	Study populations	Analysis	Sensitivity polyps any size	Specificity polyps any size	Sensitivity polyps <6mm	Specificity polyps <6mm	Sensitivity polyps ≥6mm	Specificity polyps ≥6mm	Sensitivity polyps ≥10mm	Specificity polyps ≥10mm
Meta-analyses of diagnostic accuracy of CTC											
Martin-Lopez (2013)[130]	Histological diagnosis and/or colonoscopy for verification	Mixed - some asymptomatic, some FOBT-positive, surveillance or family history	Per-patient	0.67	0.80	NR	NR	0.77 (5-7mm); 0.87 (8-10mm)*	0.87 (5-7mm); 0.90 (8-10mm)*	0.91	0.87
Bai (2020)[285]	Colonoscopy and/or histology	Symptoms of CRC, family history or positive FOBT	Per-patient	NR	NR	NR	NR	0.87	0.90	0.91	0.98
Chaparro (2009)[286]	Colonoscopy or surgery	Mixed - average risk and high risk	Per-patient	0.69	0.83	NR	NR	0.60*[‡]	0.90*	0.83	0.92
De Haan (2011)[287]	Various	Average risk - screening	Per-patient	NR	NR	NR	NR	0.76	0.95	0.83	0.99
Halligan (2005)[153]	Colonoscopy or surgery	Mostly symptomatic	Per-patient	Range = 45%–97%[‡]	Range 26%–97%[‡]	NR	NR	0.86	0.86	0.93	0.97
Lin (2021)[288]	Colonoscopy or robust registry follow-up	N/a	Unclear	NR	NR	NR	NR	0.86	0.88	0.89	0.94
Mulhall (2005)[289]	Colonoscopy or surgery	Mostly high risk	Per-patient	0.70	0.86	0.48	0.91	0.70*	0.93*	0.85	0.97
Plumb (2014)[290]	Colonoscopy, segmental unblinded colonoscopy or surgery with histopathology	FOBT positive	Per-patient	NR	NR	NR	NR	0.89	0.75	NR	NR

Author	Reference standard	Study populations	Analysis	Sensitivity polyps any size	Specificity polyps any size	Sensitivity polyps <6mm	Specificity polyps <6mm	Sensitivity polyps ≥6mm	Specificity polyps ≥6mm	Sensitivity polyps ≥10mm	Specificity polyps ≥10mm
Rosman (2007)[154]	Colonoscopy	Mixed - symptomatic, surveillance or suspected polyp	Per-patient	0.73	0.77	0.56	NR	0.63 (6-10mm); 0.77 (≥6mm)	0.84	0.82* (>10mm)	0.96
Sosna (2003)[291]	Colonoscopy	Mostly high risk	Per-patient	0.81†	NR	0.65	NR	0.84*	NR	0.88	0.95
Meta-analyses of diagnostic accuracy of colonoscopy											
Martin-Lopez (2013)[130]	Histological diagnosis and/or colonoscopy for verification	Mixed - some asymptomatic, some FOBT-positive, surveillance or family history	Per-patient	0.925	0.732	NR	NR	0.87 (5-7mm); 0.89 (8-10mm)*	0.98 (5-7mm); 0.99 (8-10mm)*	0.93	0.91
Lin (2021)[288]	Unclear	Unclear	Unclear	NR	NR	NR	NR	0.75	0.94	0.89	0.89
Van Rijn (2006)[113]	Tandem colonoscopy	Mixed - average risk and high risk	Unclear - appears to be per-polyp	0.79	NR	0.74 (1-5mm)	NR	0.87 (5-9mm)*	NR	0.98	NR
Zhao (2019)[292]	Tandem colonoscopy	Mixed - average risk and high risk	Unclear - appears to be per-polyp	0.74‡	NR	0.72	NR	0.83*	NR	0.94	NR

CT - computed tomography; FOBT - faecal occult blood tests; CRC - colorectal cancer; NR - not reported

** Estimate reflects reported value within a size interval rather above a minimum size threshold. Size interval indicated where this is not 6-9mm*

†Estimate is based on the largest polyp.

‡ Estimate reports including <6 or 1-5 polyps in the global estimate for any size polyps.

⁋ *The study reports two different estimates: 0.60 in the main text and 0.63 in Figure 5a. It is unclear which estimate is correct.*

Appendix 9: Costs of bowel preparation applied in the EAG's model

Table 68: Dosing schedule of different bowel preparation medications

Medications	Units	Cost per pack	Cost per unit	Source
Moviprep (units = sachets)	4	£14.92	£3.73	BNF 2024 (accessed 30.10.2024)
Gastrografin (units = ml)	1,000	£175	£0.18	
Phospho-soda/electrolytes (units = ml)	90	£4.79	£0.05	
Prucalopride (units = mg)	28	£32.89	£1.17	
Bisacodyl suppository (units = mg)	12	£2.99	£0.25	

Table 69: Total costs of bowel preparation (medication) by diagnostic imaging test

Test	Total units	Total cost*	Source
Colonoscopy (Moviprep)	4	**£14.92**	Total units/dosing from Medtronic.
CTC (Gastrografin)	100	**£17.50**	
CCE			
Moviprep	4	£14.92	
Gastrografin	50	£8.75	
Phospho-soda – 1st booster	30	£1.60	
Phospho-soda – 2nd booster	15	£0.80	
Prucalopride	2	£2.35	
Bisacodyl suppository	1	£0.25	
CCE total		**£28.66**	

Appendix 10: Cost-effectiveness acceptability curves

Figure 18: Population 1a: Cost-effectiveness acceptability curves for CCE, COL and CTC in the symptomatic, FIT 10-100µg/g, COL-eligible population

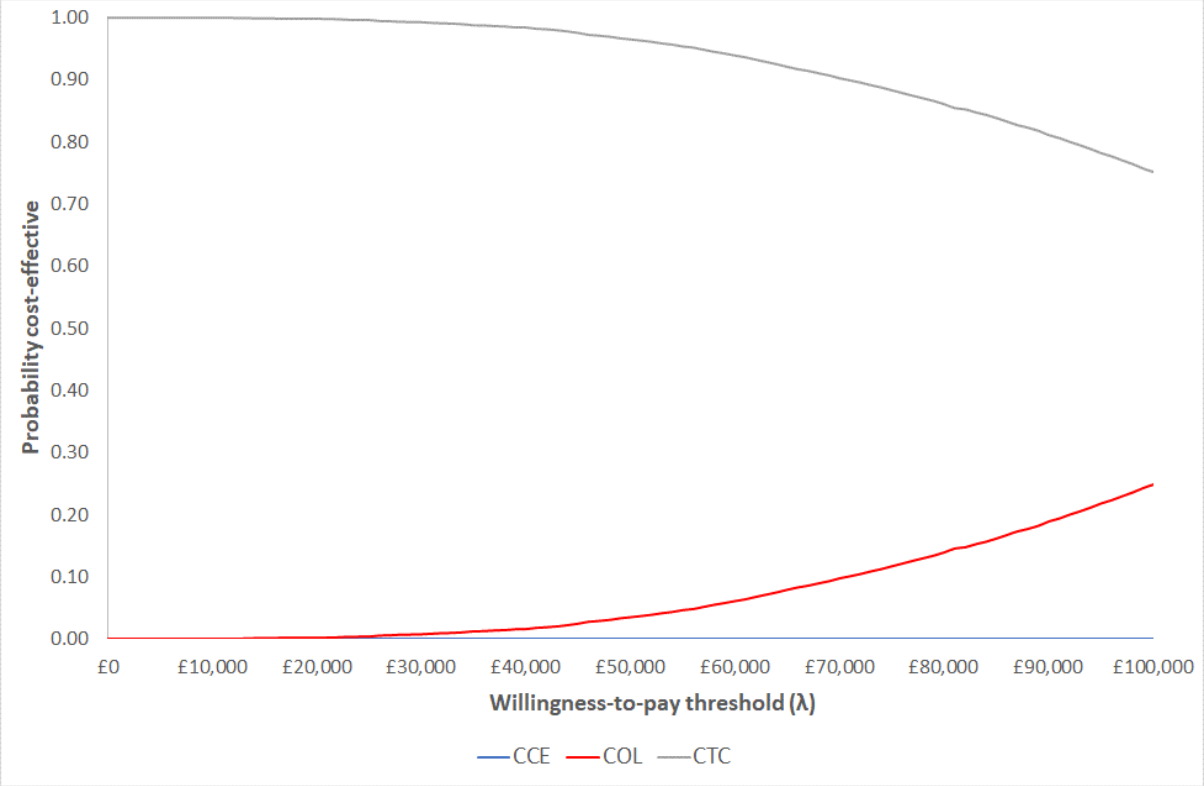


Figure 19: Population 1b: Cost-effectiveness acceptability curves for CCE and CTC in the symptomatic, FIT 10-100µg/g, COL-ineligible population

Figure 20: Population 2a: Cost-effectiveness acceptability curves for CCE, COL and CTC in the symptomatic, FIT <10µg/g, COL-eligible population

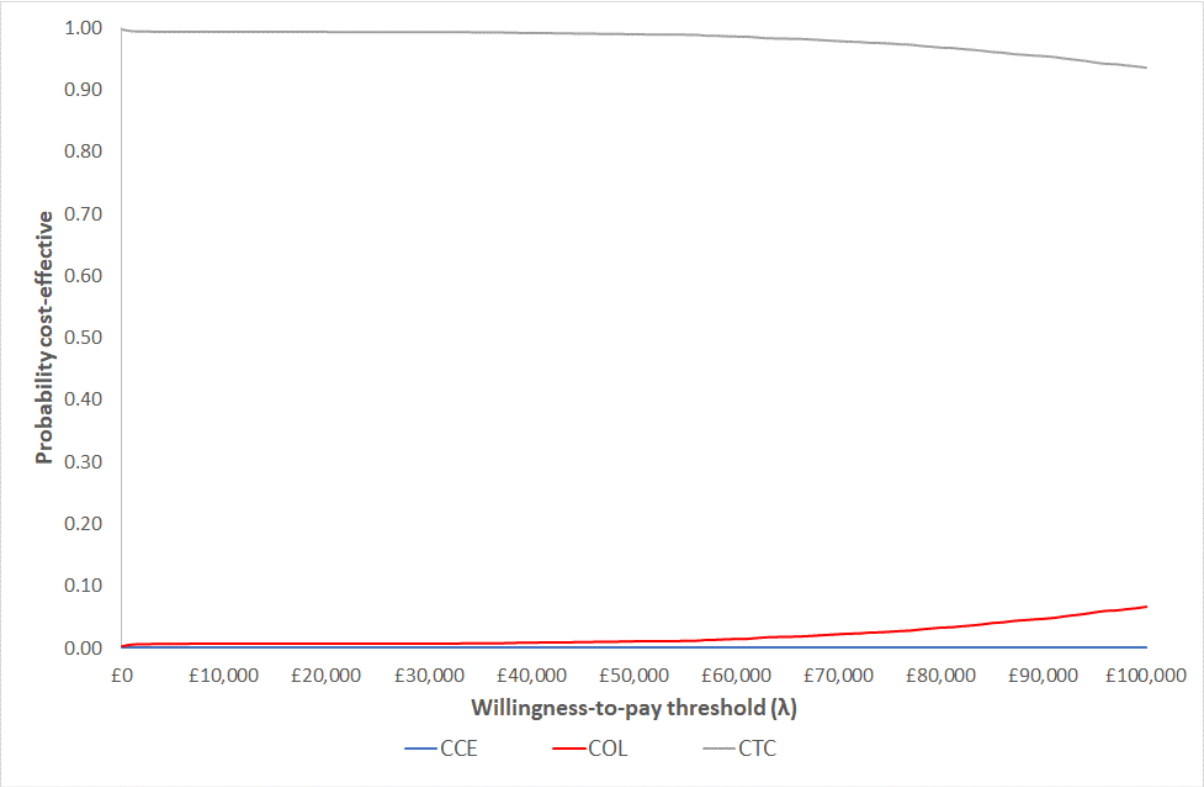


Figure 21: Population 2b: Cost-effectiveness acceptability curves for CCE and CTC in the symptomatic, FIT <10µg/g, COL-ineligible population

Figure 22: Population 3a: Cost-effectiveness acceptability curves for CCE, COL and CTC in the surveillance (post-polypectomy), COL-eligible population

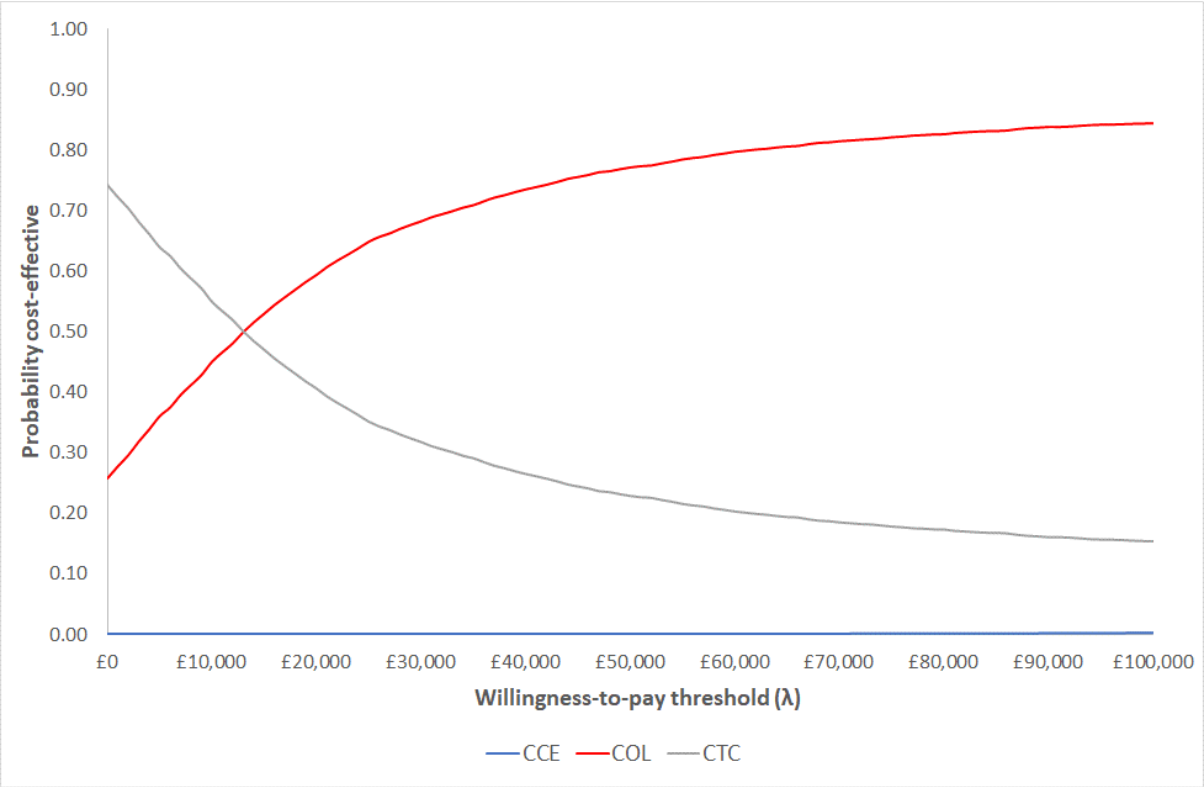
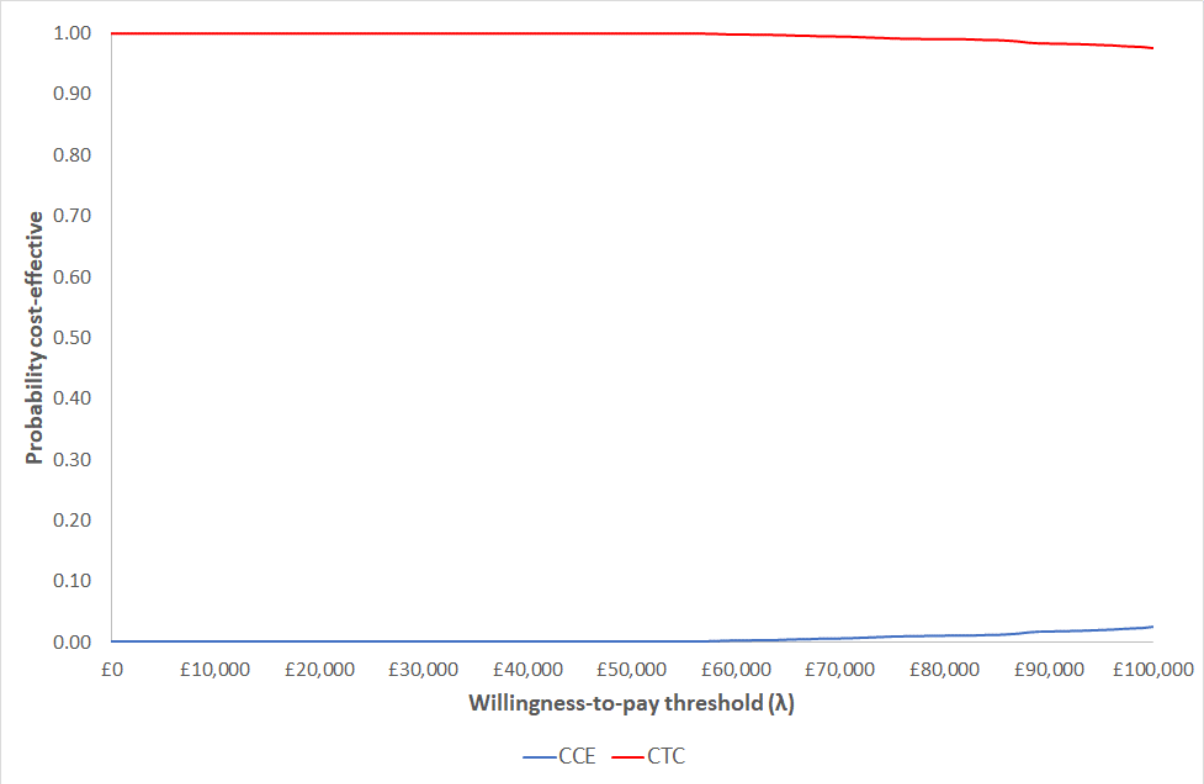


Figure 23: Population 3b: Cost-effectiveness acceptability curves for CCE and CTC in the surveillance (post-polypectomy), COL-ineligible population



Appendix 11: EAG model results - pairwise comparisons

Table 70: Central estimates of cost-effectiveness – CCE versus COL, pairwise, probabilistic

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (CCE vs comparator)	INMB WTP=£20,000/ (CCE vs comparator)	INMB WTP=£30,000/ (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
CCE	14.51	11.3501	£5,413	0.00	-0.0017	£323	**Dominated**	-£356	-£373
COL	14.52	11.3517	£5,090	-	-	-	-	-	-
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
CCE	14.60	11.4685	£2,559	0.00	-0.0005	£276	**Dominated**	-£286	-£290
COL	14.60	11.4689	£2,283	-	-	-	-	-	-
Population 3a: Surveillance (post-polypectomy), COL-eligible									
CCE	14.00	10.8797	£2,573	-0.01	-0.0084	£545	**Dominated**	-£714	-£798
COL	14.01	10.8882	£2,028	-	-	-	-	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. – incremental

Table 71: Central estimates of cost-effectiveness – CCE versus COL, pairwise, deterministic

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (CCE vs comparator)	INMB WTP=£20,000/ (CCE vs comparator)	INMB WTP=£30,000/ (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
CCE	14.50	11.3568	£5,392	0.00	-0.0015	£319	**Dominated**	-£349	-£364
COL	14.50	11.3583	£5,073	-	-	-	-	-	-
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
CCE	14.59	11.4796	£2,448	0.00	-0.0004	£271	**Dominated**	-£279	-£282
COL	14.59	11.4800	£2,177	-	-	-	-	-	-
Population 3a: Surveillance (post-polypectomy), COL-eligible									
CCE	13.99	10.9022	£2,339	-0.01	-0.0075	£538	**Dominated**	-£689	-£764
COL	14.00	10.9097	£1,801	-	-	-	-	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. – incremental

Table 72: Central estimates of cost-effectiveness – CCE versus CTC, pairwise, probabilistic

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (CCE vs comparator)	INMB WTP=£20,000/ (CCE vs comparator)	INMB WTP=£30,000/ (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
CCE	14.51	11.3501	£5,413	0.00	0.0006	646.63	**£1,055,285**	-£634	-£628
CTC	14.52	11.3494	£4,766	-	-	-	-	-	-
Population 1b: Symptomatic, FIT 10-100µg/g, COL-ineligible									
CCE	14.51	11.3493	£5,347	0.00	-0.0001	576.00	**Dominated**	-£578	-£579
CTC	14.52	11.3494	£4,771	-	-	-	-	-	-
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
CCE	14.60	11.4685	£2,559	0.00	0.0014	652.29	**£467,706**	-£624	-£610
CTC	14.60	11.4671	£1,907	-	-	-	-	-	-
Population 2b: Symptomatic, FIT <10µg/g, COL-ineligible									
CCE	14.60	11.4678	£2,476	0.00	0.0008	566.03	**£713,959**	-£550	-£542
CTC	14.60	11.4670	£1,910	-	-	-	-	-	-
Population 3a: Surveillance (post-polypectomy), COL-eligible									
CCE	14.00	10.8797	£2,573	0.00	-0.0023	629.37	**Dominat**ed	-£676	-£700
CTC	14.00	10.8821	£1,944	-	-	-	-	-	-
Population 3b: Surveillance (post-polypectomy), COL-ineligible									
CCE	14.00	10.8777	£2,581	-0.01	-0.0041	625.94	**Dominated**	-£708	-£749
CTC	14.00	10.8818	£1,955	-	-	-	-	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. – incremental

Table 73: Central estimates of cost-effectiveness – CCE versus CTC, pairwise, deterministic

Option	LYGs	QALYs	Costs	Inc. LYGs	Inc. QALYs	Inc. costs	ICER (CCE vs comparator)	INMB WTP=£20,000/ (CCE vs comparator)	INMB WTP=£30,000/ (CCE vs comparator)
Population 1a: Symptomatic, FIT 10-100µg/g, COL-eligible									
CCE	14.50	11.3568	£5,392	0.00	0.0008	£642	**£814,299**	-£626	-£618
CTC	14.50	11.3560	£4,750	-	-	-	-	-	-
Population 1b: Symptomatic, FIT 10-100µg/g, COL-ineligible									
CCE	14.50	11.3560	£5,326	0.00	0.0001	£571	**£7,208,331**	-£570	-£569
CTC	14.50	11.3560	£4,755	-	-	-	-	-	-
Population 2a: Symptomatic, FIT <10µg/g, COL-eligible									
CCE	14.59	11.4796	£2,448	0.00	0.0015	£648	**£434,488**	-£618	-£603
CTC	14.59	11.4781	£1,800	-	-	-	-	-	-
Population 2b: Symptomatic, FIT <10µg/g, COL-ineligible									
CCE	14.59	11.4790	£2,365	0.00	0.0009	£562	**£632,836**	-£544	-£535
CTC	14.59	11.4781	£1,803	-	-	-	-	-	-
Population 3a: Surveillance (post-polypectomy), COL-eligible									
CCE	13.99	10.9022	£2,339	0.00	-0.0014	£620	**Dominated**	-£648	-£662
CTC	13.99	10.9036	£1,719	-	-	-	-	-	-
Population 3b: Surveillance (post-polypectomy), COL-ineligible									
CCE	13.98	10.9002	£2,347	0.00	-0.0032	£618	**Dominated**	-£681	-£713
CTC	13.99	10.9034	£1,729	-	-	-	-	-	-

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; INMB - incremental net monetary benefit; WTP - willingness-to-pay; Inc. – incremental

Table 74 : Deterministic sensitivity analyses – CCE versus comparators, pairwise ICERs, COL-eligible groups

No.	Scenario	1a: Symptomatic, FIT 10-100µg/g, COL-eligible		2a: Symptomatic, FIT <10µg/g, COL-eligible		3a: Surveillance (post-polypectomy), COL-eligible	
		ICER (vs COL)	ICER (vs CTC)	ICER (vs COL)	ICER (vs CTC)	ICER (vs COL)	ICER (vs CTC)
-	Base case (deterministic)	Dominated	£814,299	Dominated	£434,488	Dominated	Dominated
1	Plain X-ray for all incomplete CCE tests	Dominated	£822,195	Dominated	£438,661	Dominated	Dominated
2	Pre-test CT scan for all CCEs	Dominated	£993,903	Dominated	£529,406	Dominated	Dominated
3	CCE cost = £828.36	Dominated	£932,604	Dominated	£497,010	Dominated	Dominated
4	CCE given in primary care	Dominated	£691,111	Dominated	£369,385	Dominated	Dominated
5	Patency capsule costs included	Dominated	[redacted]	Dominated	[redacted]	Dominated	Dominated
6	CCE reading time = 30 minutes	Dominated	£723,557	Dominated	£386,533	Dominated	Dominated
7	Prevalence based on FastTrack FIT	Dominated	£747,949	Dominated	£434,488	Dominated	Dominated
8	COL miss rate from Bressler *et al.*[152]	Dominated	£717,009	Dominated	£434,488	Dominated	Dominated
9	CCE diagnostic accuracy from Spada *et al.*[155]	£4,445,385	£261,933	Dominated	£366,254	Dominated	£597,735
10	CCE diagnostic accuracy equivalent to COL	£1,152,673	£231,527	£975,481	£282,212	£1,170,900	£80,761
11	CCE diagnostic accuracy from EAG meta-analysis SA1	Dominated	£410,871	Dominated	£358,032	Dominated	£251,320
12	CTC diagnostic accuracy from Halligan *et al.*[153]	Dominated	Dominated	Dominated	£690,686	Dominated	Dominated
13	CTC diagnostic accuracy from Rosman *et al.*[154]	Dominated	£161,303	Dominated	£229,875	Dominated	£32,868
14	CCE diagnostic accuracy equivalent to CTC	Dominated	£359,931	Dominated	£403,661	Dominated	£201,540
15	COL miss rates from Van Rijn *et al.*[113]	Dominated	£604,407	Dominated	£440,315	Dominated	Dominated
16	CCE completion rate = 100%	Dominated	£2,828,134	Dominated	£310,820	Dominated	Dominated
17	COL used instead of FSIG	Dominated	£821,536	Dominated	£438,792	Dominated	Dominated
18	CTC repeated for 40% of incomplete CTCs	Dominated	£803,503	Dominated	£432,551	Dominated	Dominated
19	LRAs detected by CCE/CTC not referred for 1 year	Dominated	£1,110,894	Dominated	£532,614	Dominated	Dominated
20	Improved CRC stage dist. for CCE	Dominated	£814,299	Dominated	£434,488	Dominated	Dominated
21	Diagnostic delay for missed CRC = 1.5 years	Dominated	£2,269,622	Dominated	£434,488	Dominated	Dominated
22	Diagnostic delay for missed CRC = 4 months	Dominated	£653,065	Dominated	£434,488	Dominated	Dominated
23	Long-term costs for polyps and CRCs + 25%	Dominated	£812,446	Dominated	£432,739	Dominated	Dominated
24	Long-term costs for polyps and CRCs - 25%	Dominated	£816,151	Dominated	£436,237	Dominated	Dominated
25	Surveillance CRC dist. = 75% stage A, 25% stage B	Dominated	£814,299	Dominated	£434,488	Dominated	Dominated
26	CT/MRI used following incomplete CTC (COL-ineligible)	Dominated	£814,299	Dominated	£434,488	Dominated	Dominated
27	CCE diagnostic accuracy equivalent to COL, CCE completion rate = 85%	£608,006	£188,398	£389,765	£224,052	£962,454	£71,176

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FSIG - flexible sigmoidoscopy; CT - computed tomography; MRI - magnetic resonance imaging; SA - sensitivity analysis; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; dist. - distribution

Table 75: Deterministic sensitivity analyses – CCE versus comparator, pairwise ICERs, COL-ineligible groups

No.	Scenario	1b: Symptomatic, FIT 10-100µg/g, COL-ineligible	2b: Symptomatic, FIT <10µg/g, COL-ineligible	3b: Surveillance (post-polypectomy), COL-ineligible
		ICER (vs CTC)	ICER (vs CTC)	ICER (vs CTC)
-	Base case (deterministic)	£7,208,331	£632,836	Dominated
1	Plain X-ray for all incomplete CCE tests	£7,286,818	£639,848	Dominated
2	Pre-test CT scan for all CCEs	£8,957,809	£789,118	Dominated
3	CCE cost = £828.36	£8,360,712	£735,779	Dominated
4	CCE given in primary care	£6,008,392	£525,645	Dominated
5	Patency capsule costs included	[redacted]	[redacted]	Dominated
6	CCE reading time = 30 minutes	£6,324,445	£553,879	Dominated
7	Prevalence based on FastTrack FIT	£2,491,007	£632,836	Dominated
8	COL miss rate from Bressler *et al.*[152]	£7,208,331	£632,836	Dominated
9	CCE diagnostic accuracy from Spada *et al.*[155]	£341,736	£493,506	Dominated
10	CCE diagnostic accuracy equivalent to COL	£292,452	£343,936	£117,118
11	CCE diagnostic accuracy from EAG meta-analysis SA1	£697,981	£471,935	£1,399,401
12	CTC diagnostic accuracy from Halligan *et al.*[153]	Dominated	£1,070,351	Dominated
13	CTC diagnostic accuracy from Rosman *et al.*[154]	£254,486	£312,748	£66,672
14	CCE diagnostic accuracy equivalent to CTC	£531,542	£547,098	£556,597
15	COL miss rates from Van Rijn *et al.*[113]	£7,208,331	£632,836	Dominated
16	CCE completion rate = 100%	£2,165,063	£305,665	Dominated
17	COL used instead of FSIG	£7,186,859	£630,728	Dominated
18	CTC repeated for 40% of incomplete CTCs	£7,146,953	£630,405	Dominated
19	LRAs detected by CCE/CTC not referred for 1 year	Dominated	£699,498	Dominated
20	Improved CRC stage dist. for CCE	£7,208,331	£632,836	Dominated
21	Diagnostic delay for missed CRC = 1.5 years	Dominated	£632,836	Dominated
22	Diagnostic delay for missed CRC = 4 months	£1,883,371	£632,836	Dominated
23	Long-term costs for polyps and CRCs + 25%	£7,209,860	£631,654	Dominated
24	Long-term costs for polyps and CRCs - 25%	£7,206,803	£634,019	Dominated
25	Surveillance CRC dist. = 75% stage A, 25% stage B	£7,208,331	£632,836	Dominated
26	CT/MRI used following incomplete CTC (COL-ineligible)	£11,594,497	£648,745	Dominated
27	CCE diagnostic accuracy equivalent to COL, CCE completion rate = 85%	£204,720	£238,668	£83,228

CCE - colon capsule endoscopy; COL - colonoscopy; CTC - computed tomography colonography; FSIG - flexible sigmoidoscopy; CT - computed tomography; MRI - magnetic resonance imaging; SA - sensitivity analysis; FIT - faecal immunochemical test; LYG - life year gained; QALY - quality-adjusted life year; dist. - distribution

Health Tech Programme

PillCam COLON 2 for investigation of the colon through direct visualisation

External Assessment Report - Comments collated table:

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
1	Medtronic	190	8	**We ask the EAG to consider the following studies that are relevant to this assessment:** **Accuracy and Patient Preference** Rondonotti et al[1] reported on the accuracy and patient preference of CCE compared to CTC. This study is part of the reference list but was not included in the patient preference section. The study concluded that CC2 seemed to be better tolerated than CTC and 78% of the patients preferred CC2 over CTC in all cases for the bloating/mild pain perceived during CTC. Among the 11 individuals favouring CTC, the reason for selecting CTC was the unpleasant CC2 preparation in 10 individuals, and the procedure duration in 1 individual. **Colonoscopy Capacity** A study by Holleran et al[2] concluded that CCE is a safe and effective means of detecting cancer and polyps in a positive FIT screening cohort. The results suggest that CCE would be a useful "filter test" and would reduce the number of colonoscopies performed by 71%. **Diagnostic Accuracy**	The studies reported by Rondonotti *et al.*, Holleran *et al.*, González-Suárez *et al.* and Cash *et al.* were all undertaken in exclusively asymptomatic screening populations and are therefore outside of the scope for this appraisal. As per the protocol, the EAG only included data on completion, detection and retention rates of CCE from studies that either reported diagnostic accuracy or yield. The Valdivia *et al.* review mentioned by the company does not appear to report data for PillCam COLON 2 as a subgroup, or by indication. The EAG identified Valdivia *et al.* as a potential source for inclusion in the economic model, but instead used alternative sources for aspiration and retention rates (Thorndal *et al.* and Wang *et al.*).

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
				It is unclear if the VICOCA study[3] diagnostic accuracy study comparing CCE to CTC has been included in the review: This study demonstrated that: • Colon capsule endoscopy detected more patients with any neoplastic lesion (regardless of size). • Colon capsule endoscopy is superior to CT colonography for detecting patients with significant lesions (i.e. ≥ 6mm in size at colonoscopy), with a slightly lower specificity. • Colon capsule endoscopy and CTC are well accepted, useful and safe strategies, with similar performance in terms of advanced neoplasm detection rate. However, CCE may benefit from a higher sensitivity for detecting small, flat, sessile and serrated lesions. **Diagnostic Yield** The TOPAZ study[4] reported on diagnostic yield: The proportion of subjects with any polyp ≥6 mm confirmed by OC was 31.6% for CCE versus 8.6% for CTC (pPr non-inferiority and superiority=0.999). The diagnostic yield of polyps ≥10 mm was 13.5% with CCE versus 6.3% with CTC (pPr non-inferiority=0.9954). **Indications, Detection, Completion and Retention Rates of Capsule Endoscopy** A 2022 Systematic Review and Meta-Analysis by Valdivia et al[5] evaluated performance measures such as completion, detection and retention rates of capsule endoscopy. **References:**	

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
				1. *Rondonotti E, Borghi C, Mandelli G, Radaelli F, Paggi S, Amato A, et al. Accuracy of capsule colonoscopy and computed tomographic colonography in individuals with positive results from the fecal occult blood test. Clinical Gastroenterology and Hepatology 2014;12(8):1303-10 (Ref. 223)* 2. Holleran G, Leen R, O'Morain C, McNamara D. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy. 2014 Jun;46(6):473-8. doi: 10.1055/s-0034-1365402. Epub 2014 May 13. Erratum in: Endoscopy. 2014 Jul;46(7):572. PMID: 24824091 3. González-Suárez B et al. Colon capsule endoscopy versus CT colonography in FIT-positive colorectal cancer screening subjects: a prospective randomised trial-the VICOCA study. BMC Med. 2020 Sep 18;18(1):255. doi: 10.1186/s12916-020-01717-4. PMID: 32943059; PMCID: PMC7500543 4. CASH, Brooks D., et al. Multicentre, prospective, randomised study comparing the diagnostic yield of colon capsule endoscopy versus CT colonography in a screening population (the TOPAZ study). Gut, 2021, 70.11: 2115-2122. 5. Cortegoso Valdivia, P., Skonieczna-Z et al. Indications, Detection, Completion and Retention Rates of Capsule Endoscopy in Two Decades of Use: A Systematic Review and Meta-Analysis. Diagnostics 2022, 12, 1105. https://doi.org/10.3390/diagnostics12051105	

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
2	Medtronic	103	3.4	The evidence summary section states: ***"Four studies[31-34, 40, 68, 78] reported diagnostic yield in the scope-defined populations. These studies reported the numbers of polyps identified for various size categories, but the data of perhaps most interest relate to subsequent tests and discharge rates, where COL was spared in 50%[33] to 37%[31] (n=3 studies)[31, 33, 40] of symptomatic patients, but in fewer surveillance patients at 27%[31]".*** We ask the EAG to also consider the Holleran study[1] published in 2016, this is an important relevant study. The authors conclude that CCE is a safe and effective means of detecting cancer and polyps in a positive FIT screening cohort. The results suggest that CCE would be a useful "filter test" in this situation and would **reduce the number of colonoscopies performed by 71%.** 1. Holleran G, Leen R, O'Morain C, McNamara D. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy. 2014 Jun;46(6):473-8. doi: 10.1055/s-0034-1365402. Epub 2014 May 13. Erratum in: Endoscopy. 2014 Jul;46(7):572. PMID: 24824091	As noted above, the study reported by Holleran *et al.* recruited an asymptomatic screening population and does not include any patients within the scope of this appraisal. Therefore, this study was excluded from the EAG's systematic review.
3	Medtronic	129	4.4	**Interpreting the results of the EAG's economic analysis** We would like to highlight that the EAG model estimates a negligible difference in effectiveness (as measured in quality-adjusted life-years [QALY]) between CCE, COL, and CTC across all populations considered (i.e. < 0.01 QALY difference across all populations considered, see **Table 1** below). In situations like this, using incremental cost-effectiveness ratios (ICER) for decision-making can be very misleading; for example, at present, a £100 difference in cost between CCE and a comparator	The EAG agrees that the QALY losses predicted by the model are small - this is already explained in the scientific summary, the economic results chapter and the discussion sections of the EAG report. However, the EAG does not believe that the small QALY losses predicted by the model necessarily mean that the ICERs are misleading. To aid interpretation, the EAG has presented the base case results

<table>
<tr><th>Comment no.</th><th>Stakeholder</th><th>Page no.</th><th>Section no.</th><th>Comment</th><th>EAG Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>would generate an ICER greater than £10,000 per QALY gained due to this very small difference in QALYs.

We therefore encourage the committee to look at more meaningful outcomes for CCE such as its impact on incremental costs and its ability to reduce the demand for colonoscopy within the NHS system.

NHS England reported that, at the end of March 2024, 60,217 and 180,133 patients were waiting for a diagnostic colonoscopy or CT scan, respectively; 27.4% and 12.2% of these patients had been waiting more than 6 weeks for testing and no commissioner met the NHS operating target of having < 1% of patients waiting longer than this for key diagnostic tests.

CCE is designed to alleviate these resource constraints by identifying those patients without pathology and removing them from the diagnostic pathway; this benefit of CCE is supported by the EAG model whereby its use in COL-eligible patients leads to a large reduction in the number of colonoscopies undertaken (i.e. between 34% and 67%, see Table 2 below).

It is essential that Diagnostic Advisory Committee members are provided with this information to allow them to contextualise the results of the EAG analysis.

Table 1: Base case, probabilistic, QALYs difference between CCE and comparators [Table 46 in EAR]

<table><tr><th rowspan="2">Population</th><th colspan="2">QALY difference for CCE versus comparator</th></tr><tr><th>COL</th><th>CTC</th></tr><tr><td>1a: Symptomatic, FIT 10-100µg/g, COL-eligible</td><td>0.0016</td><td>-0.0007</td></tr></table></td><td>in terms of net monetary benefit as well as ICERs (see EAG report, Tables 46 and 47). Costs for each option are also presented separately, including a breakdown by cost component.

The EAG has already presented intermediate model outcomes including the use of subsequent COL or FSIG following CCE, COL and CTC (see Section 4.3.6.2, Tables 48 and 49).</td></tr>
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<tr><th>Comment no.</th><th>Stakeholder</th><th>Page no.</th><th>Section no.</th><th>Comment</th><th>EAG Response</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>1b: Symptomatic, FIT 10-100µg/g, COL-ineligible</td><td>N/A</td><td>0.0001</td></tr>
<tr><td>2a: Symptomatic, FIT < 10µg/g, COL-eligible</td><td>0.0004</td><td>-0.0014</td></tr>
<tr><td>2b: Symptomatic, FIT < 10µg/g, COL-ineligible</td><td>N/A</td><td>-0.0008</td></tr>
<tr><td>3a: Surveillance (post-polypectomy), COL-eligible</td><td>0.0085</td><td>0.0024</td></tr>
<tr><td>3b: Surveillance (post-polypectomy), COL-ineligible</td><td>N/A</td><td>0.0041</td></tr>
</table>
Abbreviations: FIT = faecal immunochemical test; CCE = colon capsule endoscopy; COL = colonoscopy; CTC = computed tomography colonography; QALY = quality-adjusted life-year

Table 2: Model predicted reduction in colonoscopy per 1,000 patients [Tables 48/49 in EAR]

<table>
<tr><th>Population</th><th>Reduction in number of colonoscopies per 1,000 patients [CCE versus COL]</th></tr>
<tr><td>1a: Symptomatic, FIT 10-100µg/g, COL-eligible</td><td>677 (67.7%)</td></tr>
<tr><td>2a: Symptomatic, FIT < 10µg/g, COL-eligible</td><td>524 (52.4%)</td></tr>
<tr><td>3a: Surveillance (post-polypectomy), COL-eligible</td><td>348 (34.8%)</td></tr>
</table>
Abbreviations: FIT = faecal immunochemical test; CCE = colon capsule endoscopy; COL = colonoscopy
</td><td></td></tr>
<tr><td>4</td><td>Medtronic</td><td>16 & 181</td><td>1.5 & 4.4.2</td><td>Strengths and limitations of the EAG’s economic analysis

We ask that consideration is given to the additional limitations listed below:</td><td>Limitations around the diagnostic test accuracy studies included in the EAG’s meta-analysis are already discussed in Section 1.4 (page 14). Because these meta-analytic estimates are used in the</td></tr>
</table>

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
				The EAR should consider including additional perceived limitations of the economic analysis: 1. Study Design, heterogeneity of selected cohort and Sample Size Constraints resulting in limiting the generalisability of pooled sensitivity and specificity estimates. 2. The analysis assumes colonoscopy as the gold standard but lacks robust head-to-head comparisons between PillCam and alternative diagnostic modalities such as computed tomography colonography. 3. Due to limited direct evidence, mixed-population studies (some with only 11%-64% of patients falling within the NICE-defined scope), were included potentially affecting the applicability of findings to NHS-relevant populations. 4. The cost-effectiveness model assumes increased costs and lower effectiveness of PillCam without fully accounting for the potential impact of improved screening accessibility and reduced colonoscopy burden. 5. Diagnostic yield data lack confirmation of false negatives, which may impact the interpretation of test performance. We ask that the limitations outlined in the summary section are updated to better reflect the limitations section.	economic model, these limitations also impact on the model results. To avoid repetition of these points, the limitations section of the scientific summary (Section 1.5) refers more broadly to uncertainty around diagnostic accuracy estimates for CCE and comparators. The limitation regarding the diagnostic yield data not ascertaining FNs is already mentioned in Section 1.5 in reference to the clinical evidence (page 16); related to this, the uncertainty around the true prevalence of underlying pathologies in the NHSE CCE Pilot Study is already mentioned in Section 1.5 (page 16). With respect to the fourth limitation listed by the company, it is expected that the introduction of CCE will reduce the need for COL in a proportion of patients - this is already mentioned in Section 1.5 of the scientific summary as an implication for service provision. The company's comments assert that this released COL capacity could be used to improve access to CRC screening services and that not accounting for this alternative use of COL in the model is a limitation. The EAG does not consider this to be a limitation specific to this model and notes that if the COLs released by CCE were instead used for CRC screening, the model would need to include additional health benefits generated for screening participants, but the estimated cost offsets associated with avoided COLs would no longer apply for

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
					CCE (because those COLs avoided are then used in other patients).
5	Medtronic			**Negative Predictive value (NPV)** **We ask the EAG to consider the negative predictive of PillCam COLON as a tool for exclusion, as we don't have equivalent PCCRC rate for Colon capsule yet so negative predictive value (NPV) is important.** Whilst it is important that CCE is a sensitive enough test to detect pathology, **it is primarily used in low-risk patient groups as a tool to exclude pathology**. As such, CCE demonstrates a high negative predictive value (NPV) in the literature and is an important value in this low-risk patient group, allowing clinicians to exclude pathology with confidence, in the absence of a miss-rate metric such as PCCRC, as seen with colonoscopy. In time, a P-CCE-CRC rate will become established, which will demonstrate how much or how little CCE misses. This might not impact the model now, but if clinicians can exclude patients with confidence, progression to cancer could be avoided, saving the healthcare system resources and money.	The EAG's model uses estimates of prevalence, sensitivity and specificity to determine the probability that a patient is a TP, TN, FP or FN. Some of this information (TNs and FNs) could be used to calculate NPV. However, the EAG does not believe that this would be more meaningful than the analyses which have already been included in the EAG report. Sensitivity is generally considered a better metric to report in relation to diagnostic test accuracy as, unlike NPV, it is not affected by the prevalence of the disease. In relation to a test's ability to rule out disease, this can be assessed with sensitivity, as per the SNOUT and SPIN mnemonic, where a highly Sensitive test when Negative can be used to rule OUT disease.
6	Medtronic	25	2.3.1	***"The capsule captures images over a period of 10 hours or more"*** We ask the EAG to note that the NHSE Clinical Guidance document states - A study within the meta-analysis[1] found the mean capsule transit time was 4 hours and 4 minutes, and ≥70% of patients excreted the capsule within 5 hours Pecere MD et al. Accuracy of colon capsule endoscopy for advanced neoplasia. Gatrointestinal Endoscopy Volume 91, Issue 2, February 2020, Pages 406-414.e1	This paragraph of the EAG report is describing how the technology works. The information relating to the 10-hour minimum battery life is mentioned on the Medtronic website. Pecere *et al.* is one individual study which reports CCE-2 transit time undertaken in a screening population which is outside of the scope of the appraisal. The EAG also notes that whilst the mean transit time in Pecere *et al.* was around 4 hours, there is a distribution and transit time was much

Comment no.	Stakeholder	Page no.	Section no.	Comment	EAG Response
					shorter for some patients and much longer for others. The EAG does not believe that adding this text is important given the intended purpose of the paragraph.
7	Medtronic	27	2.3.4	***The EAR states: "CCE has not yet been embedded in national clinical pathways in either England or Wales".*** We ask the EAG to note that regional pathways have been established in England.	The EAG believes that the text in Section 2.3.4 is already accurate and sufficient. No amendment has been made.
8	Medtronic	66	3.3.3.1	The EAR report states: ***"The Wales Pilot Study[34] appears to have recruited patients with symptoms and a FIT of <10µg/g, designated "low-risk", but it was not clear if they were recruited using NG12 criteria"*** This is referenced in the Guidance for Clinical Vetting, Patient Selection and Bowel Preparation for the use of Colon Capsule Endoscopy (CCE) in Symptomatic Patients on a Lower Gastro-Intestinal (LGI) Pathway "Patients referred on a lower GI pathway with symptoms in accordance with current NG12 or DG30 (High risk or Low risk pathways) who are FIT negative (below a threshold of <10 µg/gm of stool)" https://executive.nhs.wales/functions/strategic-programme-for-planned-care/endoscopy/nep-docs/nep-cce-clinical-criteria/	We have changed the text to: "and it was likely, based on suggested criteria in the pilot study documentation,[ref] they were recruited using NG12 criteria."
9	Medtronic	115	4.1.1	The EAR stated: ***"conference abstracts were excluded from the main EMBASE search" and conducted a targeted search strategy to find relevant abstracts from the selection of conference series, "selected on the advice of clinical experts"*** We ask the EAG to note European Society of Gastrointestinal Endoscopy (ESGE) as another relevant conference series. There	The EAG asked its clinical advisors which were the top 4 conferences to search, and searched only those conferences. As such ESGE conference abstracts were not searched as these were not suggested by our advisors.

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				are references to ESGE in the report, so it is unclear if this was included in the congress abstract search and just missed off the list.	However, to ensure that no studies were missed, the EAG has manually downloaded and used the search facility within "ESGE Days" (which appears to be the name for the ESGE conference) for 2024, 2023 and 2022 (i.e., the last 3 years) and found no studies that met our inclusion criteria that were not already captured by the review. Terms searched included PillCam, colon capsule and capsule endoscopy.

Section B Economic model - Comments

Stakeholder	Comment	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG response
Medtronic	1	**Subsequent procedure assumptions** "Subsequent to CCE, the proportion of patients who were referred for subsequent procedures (COL, surgery, polypectomy, CTC or other	Based on the results from the NHS Pilot presented so far, the upper percentages above would appear to be an overestimate As the percentage included in the model was not disclosed, we cannot assess the appropriateness of the estimate therefore we ask the EAG to include percentage of patients referred / not referred for undergoing onward investigation from the NHS pilot study	**The expected impact after implementing the proposed amendment is:** Decrease the QALY & costs in CCE arm, resulting in lower ICER	Please note that the proportions of patients undergoing subsequent COL/FSIG following CCE (or its comparators) are intermediate outcomes estimated by the model and are not model inputs – i.e., they are a function of the other model parameters (prevalence, diagnostic accuracy and completion rates). The model-predicted proportions of patients who are referred on for COL or FSIG in the COL-

		unspecified therapies) ranged from 22% to 76%, and specifically for COL from 26% to 70%."			eligible symptomatic FIT 10-100µg, symptomatic FIT <10µg and surveillance populations are presented in Table 48 of the EAG report. The percentages of patients avoiding subsequent COL/FSIG after CCE are summarised in the text in Section 4.3.6.2. If the company has access to the results of the NHSE CCE Pilot Study, they can assess the similarity of the model predictions against the observed data from the NHSE CCE Pilot Study. [redacted]
Medtronic	2	**Decision tree colonoscopy** The model assumes that some patients with an incomplete COL will undergo a further COL rather than switching to a different test. This is not in line with current practice, where patients with an incomplete colonoscopy, would be offered a CTC **or** CCE. This is not in line with current	In Table 28 and Figure 11: Decision tree structure for colonoscopy, CTC is mentioned as a test after incomplete colonoscopy We ask the EAG to add a CCE option to the decision tree for incomplete colonoscopy and apply data from the NHS Pilot to inform this change	**The expected impact after implementing the proposed amendment is:** Increase cost and ICER of COL arm.	The EAG disagrees that CCE should be included as a replacement test following incomplete COL because CCE is not established in current clinical care in England. The structural assumptions which underpin the diagnostic pathways reflected in the decision tree model were obtained from detailed discussions with three clinical experts based in different parts of England. The advisors stated that they would try COL again if the index COL was incomplete due to inadequate bowel preparation. They also commented that COL might be re-attempted in other circumstances (e.g., under general anaesthetic if the initial COL was stopped due to

		practice and is not reflective of the NHSE pilot data. ESGE and ESGAR Guidelines recommend CTC and CCE as an alternative test, preferably the same or next day. Spada C, Hassan C, et al. Imaging alternatives to colonoscopy: CT colonography and colon capsule. European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline - Update 2020. Endoscopy. 2020 Dec;52(12):1127-1141. doi: 10.1055/a-1258-4819. Epub 2020 Oct 26. PMID: 33105507.			pain/discomfort). The study reported by Britton *et al.*, which is used to inform the proportion of patients undergoing repeat COL in the model, indicated that some patients may undergo COL again if the index COL was incomplete despite adequate bowel preparation. The EAG notes that CCE is included as a replacement test in COL-ineligible patients after incomplete CTC, as there is no alternative test. This affects a very small proportion of patients undergoing CTC (<2%) and is tested in the sensitivity analyses (DSA25). [redacted]
Medtronic	3	**CTC sensitivity smaller polyps** CTC is less sensitive for polyps	Based on the ESGE Guidance for follow-up colonoscopy the presence of at least 3 polyps of any size, is a reason for referral for diminutive polyps. Polyp multiplicity has appeared to be a strong predictive factor of	**The expected impact after implementing the proposed amendment is:**	The company's comment is accurate in that the model does not explicitly include polyp multiplicity as a predictive factor. Section 4.4.2 of the EAG report

		smaller than 6mm. These are the polyps which are also often missed at colonoscopy and can develop into cancer over 10-15 years. CCE finds many of these which colonoscopy and CTC can miss. These smaller polyps are considered as no significant bowel pathology (NSBP).	subsequent advanced neoplasia development in post-polypectomy follow-up studies[1]. The EAG model does not factor in the increased risk for polyp multiplicity which results in an underestimation of the benefit of CCE. CCE detects smaller polyps, allowing them to be removed thereby preventing them developing into larger polyps and eventually CRC. This will also be a better representation of current practice as outlined in the NHS Pilot. We ask the EAG to factor in polyp multiplicity in the economic model. 1. *Reference: Martínez ME, Baron JA, Lieberman DA et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 2009; 136: 832–841*	Increases cost in the short-term for CCE (due to extra colonoscopies for polypectomy) but prevents development of more advanced polyps and CRC in the future.	already highlights that the model considers people rather than individual polyps. However, it should be noted that the estimates of polyp prevalence in the model are drawn from data from the NHSE Pilot Study which relate to people who were referred for subsequent COL/FSIG following CCE and therefore reflects those people with polyps detected by CCE that clinicians considered to be of sufficient clinical relevance for further luminal investigation. In addition, the estimates of diagnostic accuracy applied in the model are per-person rather than per-polyp. These two factors go some way in mitigating this uncertainty. The EAG also undertook several sensitivity analyses using alternative assumptions about the diagnostic accuracy of the alternative tests, including scenarios in which the sensitivity estimates for CTC and COL in detecting smaller polyps are lower than the estimate for CCE (DSA13 and DSA15). The conclusions drawn from these scenario analyses are consistent with the EAG's base case analysis.

Medtronic	4	**Capsule Aspiration Rates and Costs** For CCE, the model includes risks associated with capsule aspiration. The risk of capsule aspiration was taken from a systematic review of aspiration rates in people undergoing **small bowel capsule endoscopy** (not CCE) reported by Thorndal et al. only a small percentage of patients experienced capsule aspiration (estimated rate of just 0.1%). In addition, no capsule aspirations have been reported in the NSHE pilot study.	The aspiration risk is taken from a systematic review in patients undergoing small bowel capsule endoscopy therefore not representative of the population in the scope. Aspiration is a rare event (estimated rate of just 0.1%[1]), and no capsule aspiration was reported in preliminary data presented on the NHSE Pilot, in over 4,000 patients. Given the rarity of this event, reporting costs of £2,908 and incident rates of 46% requiring bronchoscopy is potentially misleading. We request that the EAG removes this complication from the model. 1. Reference: Thorndal C, Selnes O, Lei II, Koulaouzidis A. A systematic review of capsule aspiration in capsule endoscopy. Ann Transl Med. 2024 Feb 1;12(1):12. doi: 10.21037/atm-23-763. Epub 2023 Aug 28. PMID: 38304904; PMCID: PMC10777238.	**The expected impact after implementing the proposed amendment is:** Small reduction in mean costs in the CCE group.	The EAG has not changed the base case analysis. In response to the company's comment, the EAG has undertaken an additional scenario analysis in which the capsule aspiration rate is assumed to be zero. The results of the analysis are very similar to the base case (see EAG addendum).
Medtronic	5	**Capsule Retention Rates and Costs** Retention rate in the model is 0.64% from Wang et al.	We ask the EAG to apply the confirmed retention rate from the NHS Pilot where the population reflects the decision problem.	**The expected impact after implementing the proposed amendment is:** Small reduction in mean costs in the CCE group.	[redacted] As such, the additional analysis requested by the company has not been conducted as the impact on the

		Most retentions are caused in the small bowel because of Crohn's Disease strictures and usually a course of steroids will relieve the inflammation and the stricture, allowing the capsule to continue.			model results would be imperceptible.
Medtronic	6	**Computed tomography colonoscopy (CTC) costs**	The EAR model applies a CTC cost of £231, which may be underestimated based on clinical feedback. Medtronic requests that the cost of CTC is updated to the NHS Payment Scheme Tariff Price of £315 (i.e. HRG code: RD61Z Colon Computerised Tomography Scan) as the most accurate cost of this test currently available.	**The expected impact after implementing the proposed amendment is:** Higher costs of diagnosis in the CTC group.	The EAG disagrees with the company's comment – the NHS Reference Costs should reflect the full cost of providing a CTC procedure (including the interpretation of the imaging results and reporting). The issue about the costs of CTC raised in the company's manuscript describing the costing model is discussed on page 182 of the EAG report and it is noted that including additional CTC reading time costs did not change the conclusions drawn from the EAG's model. Towards the end of the assessment process, updated NHS Reference Costs were published by NHS England. Notably, the more recent costs for COL and CTC are lower than the 2022/23 costs which are applied in the EAG's model. The EAG notes that including these

					lower costs would have an unfavourable impact on the economic conclusions for CCE.
Medtronic	7	**Inconsistent Costing methodology** The methodology used by the EAG to estimate the cost of the CCE and its comparators is inconsistent; specifically, a micro-costing approach was used for CCE whereas an aggregated costing approach has been used for colonoscopy and CTC. Micro-costing involves a detailed analysis and tracking of all individual cost components, capturing every small expense associated with a product or service. This often reveals hidden or overlooked costs that aggregated	We request that a consistent methodology for estimating the cost of CCE and its comparators is adopted. The aggregated cost of CCE for NHS England is captured by the Healthcare Resource Group Code: FE50A, Wireless Capsule Endoscopy, which the National Schedule of NHS Costs 2023/24 (latest reference costs) reports has a Total Unit Cost of £622. If HRGs are not used across all interventions, we suggest that micro-costing is used for all interventions	**The following impacts on economic results are expected after implementing the proposed amendment:** Total cost of CCE decreases. ICER for CCE decreases.	The EAG agrees that different approaches have been taken for estimating the costs of CCE and its comparators, but disagrees that this is a problem. Section 4.4.10 of the NICE Methods Manual highlights that data based on HRGs may not be appropriate in all circumstances, and the Methods Manual does not stipulate that the same costing approach has to be used for all interventions included in an economic evaluation. With regards to the current appraisal, the EAG believes that the NHS Reference Costs represent the most appropriate source for the costs to the NHS of providing COL and CTC procedures. Whilst a unit cost is available from the NHS Reference Costs for wireless capsule endoscopy (FE50A), this cost estimate may not specifically relate to PillCam COLON 2 and the EAG understands that other types of capsule endoscopy are currently used for non-cancer pathways in the NHS. As such, the EAG believes that it is more appropriate to use CCE costs provided by the manufacturer in the base case analysis. This issue is discussed in Section

		approaches might miss. In contrast, aggregated costing methods typically use averages or estimates, which can smooth out or overlook smaller, detailed costs, potentially underestimating true expenses.			4.2.2 of the EAG report (page 122). The EAG also notes that the sensitivity analyses presented in the EAG report include a scenario in which the NHS Reference Cost for wireless capsule endoscopy is used in the model. The economic conclusions drawn from this analysis are consistent with the base case analysis.
Medtronic	8	**Scenario Analyses – Costs and QALYs** In the deterministic sensitivity analyses, it would be helpful to see the mean costs and QALYs in each group, rather than just the ICERs.	We request that the EAG include the mean costs and QALYs for the various sensitivity analyses undertaken.	**The expected impact after implementing the proposed amendment is:** This would allow the committee to understand the effect of each scenario upon costs and QALYs. Presenting only the ICERs does not allow the full impact of model changes to be understood, particularly as the QALY differences between treatment groups are very small (leading to high ICERs).	The EAG did not present disaggregated costs and QALYs for each diagnostic option in each DSA in the EAG report as this would have resulted in very large and cumbersome tables which would be difficult to interpret. However, following the company's request, the EAG has provided these disaggregated costs and QALYs (see addendum).
Medtronic	9	**Presentation of the results of the probabilistic sensitivity analysis**	We request that the EAG provides a graphical representation of the output of the probabilistic sensitivity analysis as a scatterplot of incremental costs and QALYs.	**The expected impact after implementing the proposed amendment is:** The availability of this visual aid will facilitate an	The EAG did not present the results of the PSA using cost-effectiveness planes as these plots are not interpretable in the context of fully incremental analyses which include more than two interventions.

		The EAG did not provide a graphical representation of the output of the probabilistic sensitivity analysis as a scatterplot of costs and QALYs on the cost-effectiveness plane. We think providing this would be a very helpful visual aid for the committee in understanding the negligible difference in effectiveness (as measured by QALYs) between CCE, COL, and CTC, and the uncertainty regarding these estimates of effectiveness.		understanding of the negligible difference in effectiveness between CCE, COL, and CTC, and the uncertainty regarding these estimates of effectiveness. This would allow a more objective assessment of the distribution of cost and QALY differences, rather than relying on the ICERs (which fluctuate greatly due to small QALY differences).	The EAG also notes that adoption decisions should be made based on the expectation of the mean and it is clear from the base case results tables in the EAG report that the QALY losses for CCE are small (Tables 46 and 47). This finding is also explained in the text throughout the report. To address the company's comment, the EAG has produced rankograms which summarise the fully incremental PSA results by showing the probability that each diagnostic option generates the most QALYs and the probability that each diagnostic option results in the highest costs (see addendum). The plots were generated based on the same 5,000 probabilistic samples used to generate the base case results in the EAG report. These rankograms indicate the following: • In all COL-eligible populations, the probability that CCE generates the most QALYs is 0.14 or lower. • In COL-ineligible populations, the probability that CCE generates the most QALYs in the symptomatic FIT 10-100µg/g, symptomatic FIT

					<10µg/g and surveillance populations is 0.52, 0.90 and 0.26, respectively. • Across all COL-eligible and COL-ineligible populations, the probability that CCE results in the highest costs is approximately 1.0.
Medtronic	10	**Change in Pilot Outcomes Over Time** The size of polyps was overestimated in the initial stages of the CCE pilot, which resulted in a higher negative rate for follow on colonoscopies.	Learning curve, improved patient selection, reading & reporting and improvement in bowel prep resulted in fewer follow-on colonoscopies in the latter half of the NHS Pilot therefore the latest year of the pilot is more representative of current CCE practice. We ask the EAG to describe the improvements in CCE outcomes over time in the pilot and to use the outcomes post changes in bowel prep to inform the base-case.	**The expected impact after implementing the proposed amendment is:** Improved completion rates in the CCE group, leading to lower costs due to avoidance of further diagnostic tests.	This issue may be relevant to decision-making. However, the EAG does not have access to this information. The model is informed by data which were provided in summary form by the NHSE CCE Pilot Study Investigators. These data relate to the overall pilot study period, rather than the latter part of it. However, the EAG has already conducted scenario analyses in Table 52 whereby the CCE completion rate is assumed to be 100% or 85% (see DSA16 and DSA27). The latter scenario also includes more optimistic assumptions about the diagnostic accuracy of CCE. The conclusions of the analysis remain unchanged in both scenarios.

Medtronic	11	**NHS Capacity Constraints** The model structure used by the EAG does not account for current colonoscopy and computerised tomographic colonography (CTC) resource constraints across the NHS despite such capacity constraints being an explicit component of the research question for this report. NHS England reported that, at the end of March 2024, 60,217 and 180,133 patients were waiting for a diagnostic colonoscopy or CT scan, respectively; 27.4% and 12.2% of these patients had been waiting more than 6 weeks for testing. CCE is designed to alleviate these	At present, the model implicitly assumes that there are no resource constraints across the NHS, which directly contradicts figures provided by NHS England as noted above. By omitting this capacity releasing aspect from the model, the value of CCE to the NHS is significantly underestimated. We ask that the model structure is adapted to account for this capacity releasing aspect of CCE. We anticipate that this could be incorporated by imposing a penalty for comparators in the form of a 'stage-shift' in colorectal cancer, risk of increased growth or malignant transformation of adenomas, or increased severity of non-malignant inflammatory bowel disease. This approach would be consistent with that already used in the model for misdiagnosis.	**The following impacts on economic results are expected after implementing the proposed amendment:** Comparator (COL, CTC) quality-adjusted life-years (QALYs) decrease. Incremental cost-effectiveness ratio (ICER) for CCE decreases.	The company's comment is accurate with respect to the base case analysis. The potential benefits of released COL capacity are however already included in a scenario analysis in Table 52 (DSA20). [redacted] the results were unchanged from the base case. This issue is already discussed in Section 4.4.2 of the EAG report (pages 182-183).

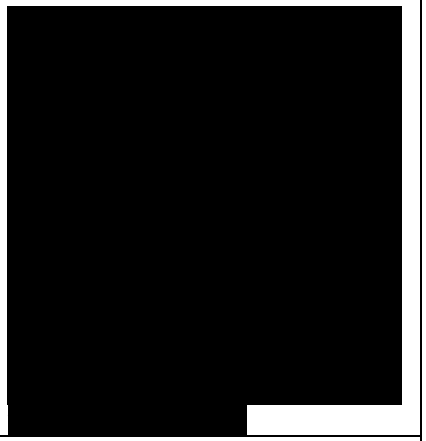
		resource constraints by identifying those patients without pathology and removing them from the diagnostic pathway.			
Medtronic	12	**Assumptions LRA and AA removed at index / replacement test** The model assumes that all LRAs can be removed immediately at the index or replacement COL/FSIG. Therefore, no additional confirmatory test is	Not all polyps are removed during the index colonoscopy as some of the colonoscopies are done by HCPs who cannot perform polypectomies; therefore, some patients require an additional colonoscopy to perform the polypectomy. There is also a significant amount of outsourcing colonoscopy activity in NHS England, and these are mainly diagnostic therefore a percentage of these patients will also require an additional colonoscopy for polypectomy. We ask the EAG to model the additional colonoscopies required in these scenarios, based on expert feedback and information from the CCE pilot if available.	**The expected impact after implementing the proposed amendment is:** Costs will increase in the COL group because of the need for a further COL in some patients (due to either lack of expertise or 'complex' polyps at the index COL).	The EAG's clinical advisors commented that independent UK endoscopists require accreditation from the Joint Advisory Group on GI Endoscopy (JAG) based on defined criteria (see https://thejag.zendesk.com/hc/en-us/articles/115004038674-Colonoscopy-application-criteria-and-process). This accreditation requires competence in polyp removal up to SMSA Level 2 (see Gupta *et al.*, [Gut, 2011] for details). This encompasses most polyps up to 2cm. The clinical advisors noted that there may be complexities/technical challenges which may limit an individual endoscopist removing such

		required for these patients. For patients with AAs undergoing COL/FSIG, the model assumes that 90% of these can be removed by polypectomy during the index/replacement test, whilst the remaining 10% are "complex polyps" which require a subsequent COL/FSIG procedure (p141)			polyps at the index examination, but in practice most should and would be removed. The clinical advisors agreed with the company's comment about outsourcing COL, where it may be more likely that some polyps >1cm are left *in situ* when identified. In order to address the company's comment, the EAG has undertaken additional exploratory analyses assuming that 20% or 30% of AAs require a second COL procedure. The conclusions of the analysis remain consistent with the base case (see addendum).
Medtronic	13	**Completion rates for CTC in the model** Table 36: Completion rate of 98% for CTC was applied in the economic model (Deding et al [133]). This assumption of only 2% requiring repeat testing is optimistic. This systematic review included only studies in patients who'd had	In our own model (shared with EAG as AIC) we estimated that a significantly higher percentage of CTC patients (estimated 18%) would require repeat testing (based on expert feedback). We ask the EAG to amend completion rates to reflect those in the NHS England Pilot study	**The expected impact after implementing the proposed amendment is:** Increase costs of further diagnostic testing in the CTC group.	Please note that the company's executable model was not shared with the EAG and therefore a full critique of its underlying assumptions could not be undertaken. The manuscript describing the model was shared together with a supplementary appendix. [redacted] As highlighted by the company, the systematic review Deding *et al.* which is used to inform the EAG's model included studies of

		an incomplete COL. This presents a potential bias that influences the high completion rates mentioned in this review.			CTC in people who had an incomplete prior COL. A further systematic review on the performance of CTC in patients aged ≥65 years based on 20 studies (12,936 patients) reported a pooled rate of inadequate CTC examinations of 2.0% (95% CI, 1.0 to 3.8%) (Pickhardt *et al. AJR Am J Roentgenol*, 2018). This estimate is very similar to the value reported by Deding *et al.* To address the company's comment, the EAG has undertaken an additional exploratory analysis in which 5.25% of CTCs are assumed to be incomplete, based on the SIGGAR RCT which compared CTC versus COL in patients with symptoms suggestive of CRC (Atkin *et al.*, Lancet, 2013). This estimate includes people referred for further investigation after either adequate or inadequate CTC where no pathology was seen at CTC. A further analysis assuming a rate of 18% was also conducted, based on the rate used in the company's costing model; the EAG notes this value is substantially higher than that suggested by other sources. The conclusions of these analyses remain unchanged from the base case (see addendum).

Medtronic	14	**Completion rates for CCE procedures** The EAG model uses an unknown data cut from the NHS England CCE Pilot Study to estimate the completion rate of CCE procedures. We are unable to verify the reasonableness of this assumption as it has been redacted in the EAG report; however, it is important that the data used to inform this assumption account for a change in bowel preparation (prokinetic agent was changed to procalopride in May 2022) protocol that occurred during the Pilot Study that led to significantly improved CCE completion rates.	Improved completion rates with the new bowel preparation regimens may reduce repeat testing for CCE We request that the completion rates for CCE procedures used in the base case economic results is informed by data from the NHS England Pilot Study *after* the change in bowel preparation protocol, as this is now the standard of care.	The following impacts on economic results are expected after implementing the proposed amendment: • CCE total costs decrease • CCE total QALYs increase. ICER for CCE decreases.	The EAG's base case analysis uses the overall CCE completion rate based on the data provided from the overall NHSE CCE Pilot Study. We also included separate scenario analyses in which the completion rate was assumed to be 100% or 85% (DSA16 and DSA27). The conclusions drawn from these analyses remain consistent with the EAG's base case.

Medtronic	15	**Risk Assumptions LRA and AA post Polypectomy** Diagnosed low-risk adenoma (LRA) and advanced adenoma (AA). People with diagnosed LRAs and AAs who undergo polypectomy are assumed to have the same colorectal cancer (CRC) risk as the general population.	Literature[1,2] suggests that individuals with a history of polyps may be at higher risk of developing future polyps or CRC, either due to an underlying predisposition or incomplete polypectomy. This assumption may underestimate the potential benefit of CCE in identifying and managing these patients. We ask the EAG to adjust the model inputs to assumptions to regarding the disease states for this population to reflect that they do not have the same risk as the general population. 1. Johnstone M, et al. (2023). Risk stratification for the detection of metachronous polyps after bowel screening polypectomy: clinical outcomes from the Integrated Technologies for Improved Polyp Surveillance (INCISE) study cohort. Available online here: https://pubmed.ncbi.nlm.nih.gov/37158435/ British Society of Gastroenterology. (2019). BSG/ACPGBI/PHE post-polypectomy and post-colorectal cancer resection surveillance guidelines. Full guidelines available to download online here: https://www.bsg.org.uk/clinical-resource/list-of-recommendations	**The expected impact after implementing the proposed amendment is:** Change the long-term utilities, cost and ICERs in the model.	The 2020 ESGE post-polypectomy guidelines state that based on a series of cohort studies, the overall long-term CRC risk following polypectomy appears to be similar or slightly higher than that for the general population or for patients without adenomas. The 2020 BSG/ACPGBI/PHE post-polypectomy guideline states that not all patients with previous polyps are at an increased risk of future CRC and notes that due to polyp clearance, many are at a lower risk than the general population. The EAG's model assumes that patients with detected polyps have these removed by polypectomy and that their health outcomes at this time point become the same as those for the general population. This is a simplifying assumption which is already discussed in Appendix 7 of the EAG report. Given the modelling approach adopted, the EAG is unable to provide robust estimates of the impact of incorporating polyp history into the long-term payoffs applied in the decision tree, as has been requested by the company. As discussed in Appendix 7 of the EAG report, this a minor limitation which is very unlikely to have a material impact on the economic conclusions for CCE.

Medtronic	16	**Intermediate-risk (IR) category** The external assessment group (EAG) model does not include an IR category, whereas the Medtronic model does. This distinction was incorporated based on clinical feedback on real-world practice through the pilot study.	Not including an IR category may underestimate the long-term benefits of CCE, as patients identified as IR in clinical practice typically undergo additional follow-up rather than being discharged. This could lead to an underestimation of CCE's impact on early detection and CRC prevention We ask the EAG to include an intermediate risk category in the model.	**The expected impact after implementing the proposed amendment is:** Change the long-term utilities, cost and ICERs in the model.	As discussed in Section 4.4.2 of the EAG report, the EAG's model is informed by MiMiC-Bowel which does not include an intermediate-risk group. If the EAG's model had included an intermediate-risk group in the decision tree, it would not be possible to estimate outcomes or costs using MiMiC-Bowel and it is unclear what alternative source could be used. 
Medtronic	17	**Definitions and Mapping of Risk categories** The definitions of high-risk (HR) and low-risk (LR) groups in the EAR model may not align well with the decision problem considered.	How the definitions of HR and LR map to "LRA" and "AA" within the model is not clear. If these definitions do not reflect real-world clinical categorisations, cost-effectiveness estimates may be less applicable to decision-making. We ask the EAG to provide a clearer mapping of model definitions to clinical pathways to improve transparency.	**The expected impact after implementing the proposed amendment is:** Clarifications of model definitions	Limitations relating to the definition of and correspondence between polyp risk/size categorisations are already discussed in Section 4.4.2 (page 181, first bullet point). For brevity, these points are not reiterated here.

Medtronic	18	**Diagnostic Delay Assumptions** It is assumed in the model that fixed diagnostic delays of 8 months for CRC and 36 months for polyps are applicable. Fixed diagnostic delay assumptions may not reflect real-world variation. Whilst CRC delay is varied in scenario analysis, polyp delays are based on the upper estimate sourced from Whyte et al. By using the upper estimate from the Whyte study, the model may overestimate the time between initial presentation and eventual diagnosis, leading to an overestimation of disease progression. Additionally, it does not account for the fact that some of these individuals may become eligible for Bowel Cancer Screening	Using the upper estimate may overstate disease progression and does not account for individuals who may become eligible for the Bowel Cancer Screening Programme (BCSP) within this period. It is unclear why the upper estimate was chosen. and why uncertainty wasn't explored. We ask the EAG to explore 12 months / 24 months diagnostic delay (for polyps) in the sensitivity analysis.	**The expected impact after implementing the proposed amendment is:** Change the long-term utilities, cost and ICERs in the model.	The EAG notes that there is considerable uncertainty around the duration of diagnostic delay for missed polyps and that estimates included in the model necessarily rely on clinical expert opinion. As noted in Section 4.3.2.3 of the EAG report (page 136), the EAG's base case model assumes that the average length of the delay in correcting a misdiagnosis is 8 months for CRC and 36 months for polyps. As explained in the EAG report, these estimates were informed by input received from the EAG's clinical advisors, with the estimate for polyps based on the maximum value from the analysis reported by Whyte *et al.* (contained in Appendix 7 of the EAG report). The EAG's clinical advisors commented in particular that polyps can remain undiagnosed for many years. Many polyps do not bleed or cause symptoms and therefore they may remain undiagnosed for a long time, even amongst people participating in CRC screening. However, to address the company's comment, the EAG has undertaken two additional analyses which assume that missed polyps are picked up at either 12 or 24 months. The conclusions of these analyses

		Programme (BCSP) during those three years, which could lead to earlier detection. The starting age of the population is redacted, so it is unclear whether this is applicable.			are consistent with the base case analysis (see addendum).
Medtronic	19	**Colonoscopy Specificity** The specificity of colonoscopy was assumed to be 100% for all underlying pathologies, due to the nature of the test. This assumption is in line with previous models.	We acknowledge that COL is gold standard, CCE can find polyps that COL can't find therefore COL procedures can sometimes give false negative results or consider CCE findings as false positives when not confirmed by colonoscopy. We ask the EAG to test this specificity assumption.	**The expected impact after implementing the proposed amendment is:** Change the long-term utilities, cost and ICERs in the model.	The EAG notes that the company's comment seems to relate to sensitivity rather than specificity. Parameter values relating to the sensitivity of CCE, COL and CTC have already been tested across a range of scenario analyses (DSA8-15 and DSA27). The conclusions drawn from these analyses remain consistent with the base case analysis. Additional analyses have not been conducted in response to this comment.
Medtronic	20	**Patency Capsule** The use of a patency capsule is modelled in scenario analysis. A patency capsule is used for patients with suspicion of strictures/risk of retention, which are mainly IBD patients, therefore PillCam COLON should not require	We ask that the scenario analysis around patency capsule is removed as not relevant to the review population and adding unnecessary cost to the CCE arm.	**The expected impact after implementing the proposed amendment is:** Reduction in cost in the CCE arm	The EAG disagrees with the company's comment. The use of patency capsules was discussed by stakeholders during the scoping workshop and is included in the final NICE scope for the appraisal. The EAG believes that the use of patency capsules represents one potential means of mitigating retention risk and the NICE Appraisal Committee may be interested in the results of this scenario analysis. Consequently, the EAG has not

		one. This is supported by the NHSE CCE pilot Clinical Guidance documents for symptomatic and post-polypectomy surveillance cohort exclusions. Whilst the CE mark for the use of patency capsule has been extended for use in PillCam COLON, it should only need to be used with PillCam SB3 and PillCam Crohn's capsules.			removed the analysis from the report. It should be noted that this scenario analysis assumes that only a small proportion of patients will require a patency capsule (14% based on O'Hara *et al.*) and the impact on the model results is minor.
Medtronic	21	**Model responsiveness** When the average age parameter is changed, model outcomes remain the same.	This suggests that the long-term model is not responsive to changes in patient characteristics. The use of long-term payoffs independent of key demographic factors limits the model's ability to capture age-related differences in health outcomes and costs. We ask the EAG to acknowledge this as a limitation	**The expected impact after implementing the proposed amendment is:** Additional narrative on model limitations	As described in Section 4.3 of the EAG report, the EAG's analysis combines a short-term decision tree describing diagnostic pathways for CCE, COL and CTC with long-term payoffs obtained from separate re-analyses of the MiMiC-Bowel screening model for a given population age. If it was necessary to update the age parameter in the EAG's model, then it would also be necessary to re-run MiMiC-Bowel to re-estimate the payoffs for a population of that age. However, the EAG's model, including the long-term payoffs, already reflects the mean age of patients in the NHSE CCE Pilot and so

					further re-analyses of MiMiC-Bowel are therefore unlikely to be relevant to the decision problem. The EAG does not consider this to be a relevant limitation of the model.