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

NIHR Reference Number - NIHR136010

PillCam COLON 2 for investigation of the colon through direct visualisation – Final Protocol

Version date: 06/09/2023

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2. Plain English Summary

Colorectal (bowel) cancer is the fourth most common cancer and the second most common cause of cancer death in England. Around 34,500 people in England are diagnosed with bowel cancer each year and around 13,700 people in England die from the disease each year.[1] Risk factors for bowel cancer include age, family history, genetic conditions such as Familial Adenomatous Polyposis (FAP) and Lynch syndrome, inflammatory bowel disease (IBD), and diet and lifestyle factors. Earlier detection of bowel cancer is thought to be associated with improved survival.

Most colorectal cancers arise from a prior adenomatous polyp in the bowel.[2] Colorectal polyps are very common and can be found in one in four people aged 50 years or older.[3] A polyp is a growth of tissue in the inner lining of the bowel which projects into the lumen of the bowel. A person may have one or several polyps and they are slightly more common in men. The exact cause of polyps is not known. Not all polyps turn into cancer. Certain types of adenomas, for example those with a villous growth pattern, have a higher chance of becoming cancer. Removing polyps can reduce the risk of colorectal cancer by up to 90%.[4]

The NHS bowel cancer screening programme is currently using Faecal Immunochemical Testing (FIT) in people aged 60 to 74 years. People may also present to their General Practitioner (GP) with symptoms of bowel cancer and may receive a FIT test.[5] Some people present directly to Accident and Emergency with acute symptoms, such as bowel obstruction. People with a positive FIT screening test result and those with alarming symptoms or signs of bowel cancer are referred for further investigation in secondary care. Depending on local capacity, clinical prioritisation and patient factors, further tests may involve different types of colonic imaging including optical colonoscopy, computed tomography colonography (CTC) and colon capsule endoscopy (CCE). Colonoscopy is the gold standard colonic imaging method for people on the urgent suspected cancer referral pathway. However, some people are unsuitable for or unwilling to undergo colonoscopy. Sometimes the colonoscopy is incomplete as it does not provide a full visualisation of the entire bowel. In each of these instances, an alternative investigation using CTC or CCE may be considered. Most people who undergo colonic imaging will not have polyps or cancer. NHS endoscopy services are constrained and waiting times for colonoscopy are long. This situation has worsened since the COVID-19 pandemic began. In addition, colonoscopy is associated with risks of complications including bleeding and perforation. The use of CTC and CCE may help to reduce pressures on endoscopy services. These other investigations also carry a risk of complications.

PillCam COLON 2 is a second-generation CCE technology which was launched in 2010. The technology allows for the direct visualisation of polyps, cancer and other problems in the bowel. CCE is less invasive than optical colonoscopy and does not require sedation before the procedure. CCE is already used in some centres in England, for example, for some people who are unable to undergo colonoscopy.[6,7]

This assessment will review the available evidence on the clinical effectiveness and cost-effectiveness of PillCam COLON 2 for the detection of abnormal pathology in the bowel, including polyps, cancer and other IBD. The systematic review will identify all relevant evidence relating to diagnostic accuracy, uptake, harms and other intermediate, clinical and patient-reported outcomes. The economic assessment will involve a review of previous economic evaluations of PillCam COLON 2 and the development of a new health economic model to determine whether the intervention represents good value for money for the NHS.

3. Decision problem

3.1 *Purpose of the decision to be made*

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?"*

This project will involve undertaking a systematic review and synthesis of evidence on the clinical effectiveness, diagnostic accuracy and safety of PillCam COLON 2, a type of colon capsule endoscopy (CCE). The assessment will also include a systematic review of existing economic analyses of PillCam COLON 2 and the development of a *de novo* health economic model. The assessment will focus on the anticipated use of PillCam COLON 2 in two main populations: (i) adults with lower gastrointestinal symptoms suggestive of colorectal cancer who have been referred from primary care for further colonic imaging in the symptomatic endoscopy service, and (ii) adults who are due to have a post-polypectomy surveillance colonoscopy at 3-years because of high-risk findings at their index colonoscopy.

3.2 *Clear definition of the intervention*

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 bowel cancer, Crohn's disease and ulcerative colitis). Several CCE technologies are available. This assessment will focus on one particular technology – PillCam COLON 2 (Medtronic). Other CCE technologies were considered but were excluded from the final NICE scope; these will not be 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 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 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 (SUPREP® liquid and additional laxatives) 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 colon. 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 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.

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.

3.3 *Populations and relevant subgroups*

This assessment will focus on two populations:

- 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 10-100µg/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 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.

Clinical experts have advised NICE that the technology is not appropriate for use in people with a rectal or anal mass or anal ulceration and that these patients should be excluded from the scope.

3.4 *Place of the intervention in the treatment pathway*

The 2020 European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) updated guideline on the use of imaging alternatives to colonoscopy suggests the use of CCE for faecal occult blood test (FOBT) or FIT test positive cases with incomplete or unfeasible colonoscopy, and for patients with non-alarm symptoms in whom colonoscopy 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 colonoscopy is incomplete.[8] CCE is already used as a colonic imaging modality for certain patients in some centres in England. The focus of this assessment will be on the use of PillCam COLON 2. The technology may provide an alternative to colonoscopy or CTC to rule out polyps or bowel cancer or may be used as a filter or triage test prior to colonoscopy.

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.[8, 9] The use of PillCam COLON 2 in this setting will not be considered within this assessment.

3.5 *Relevant comparators*

There are two comparators for CCE: optical colonoscopy and CTC. Optical colonoscopy involves the insertion of a long, thin, flexible tube with a small camera inside into the rectum to directly visualise the rectum and colon. Colonoscopy may be diagnostic or therapeutic; the former allows only for visualisation of the bowel and/or a biopsy to be taken whereas the latter allows for polyps to be removed at the point of detection using snare diathermy. CTC, which is also sometimes called virtual colonoscopy, uses CT scanning to take hundreds of detailed cross-sectional images of the colon and rectum. Both colonoscopy and CTC require bowel preparation before the procedure. In a diagnostic setting, colonoscopy is the gold standard imaging modality. However, some people are unsuitable for or unwilling to undergo colonoscopy (e.g., older, frail patients) and people in whom a complete colonoscopy is not achieved may require further investigation. For these people, CTC is sometimes used. Some people may not be suitable for colonoscopy or CTC and may undergo other less invasive diagnostic interventions (e.g., CT scans).

3.6 *Outcomes*

The NICE scope[10] lists the following outcomes:

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:
    - 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.

Clinical outcomes:

- 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 (AEs) associated with CCE, colonoscopy and CTC
- Mortality.

Patient-reported outcomes:

- Health-related quality of life (HRQoL)
- Anxiety associated with waiting for procedures or test results because of diagnostic delays, and further diagnostic workup
- Preference for CCE versus colonoscopy or CTC.

Health economic outcomes

Costs will be considered from an NHS and Personal Social Services (PSS) perspective. The cost-effectiveness of interventions will be expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. Costs for consideration will 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 AEs from the procedure or further diagnostic work up, including those associated with false test results and inappropriate investigations.

3.7 *Issues for consideration*

Setting for CCE delivery

During the NICE scoping workshop, there was some discussion around the appropriate setting in which CCE could be delivered. Principally, this issue concerns where the capsule is swallowed and what type of health care specialist supervises the patient whilst the capsule is swallowed. The setting in which the capsule is swallowed may impact on uptake/acceptability rates and costs, and will have implications for managing potential risks associated with swallowing (e.g., bronchial aspiration). We will explore the potential impact of alternative delivery settings (supervised swallowing of the capsule in secondary care versus community settings) on the cost-effectiveness of PillCam COLON 2.

Reading the recorded data

During the scoping workshop, it was highlighted that different types of healthcare professional may be able to read the data from the capsule, for example, specialist nurses or specialist doctors (gastroenterologists or bowel surgeons). It was also highlighted that the recorded capsule data can be uploaded onto the cloud with analysis and interpretation outsourced to centralised reading hubs. We envisage that the economic analysis will focus on scenarios in which specialist doctors and/or specialist nurses read the data; this will be clarified with clinical experts as part of the assessment.

Anticipated limitations in the available published evidence on diagnostic accuracy

A recent systematic review of CCE conducted in 2020 on behalf of the Scottish government[11] identified limited published evidence on the diagnostic accuracy of CCE in people with symptoms of bowel cancer who had previously received a positive FIT result. In order to assess the cost-effectiveness of PillCam COLON 2 in the subgroups listed in the NICE scope, we may

need to assume that the available published evidence on diagnostic accuracy can be generalised to other populations (i.e., those who have received a FIT).

The NHS England pilot study

There is an ongoing pilot study funded by NHS England which is assessing the diagnostic accuracy of CCE using PillCam COLON 2 in people who are at an intermediate (FIT-based) risk of bowel cancer or in people who are undergoing post-polypectomy bowel surveillance.[12] This study is expected to report in 2024. The data from this pilot study are likely to be highly relevant to decision problem for this appraisal. We will request interim data from the ongoing pilot from the Principal Investigator of the study for inclusion in the clinical review and the economic model.

3.8 *Areas that are outside the scope of the evaluation and therefore do not require any detailed assessment (e.g., key factors for which evidence is already accepted).*

The following will be excluded from this appraisal:

- People who have been referred for endoscopy following a positive screening test completed through participation in the English bowel cancer screening programme
- People with a rectal or anal mass or anal ulceration.
- The use of other CCE devices, including the first generation of the PillCam COLON technology
- The use of artificial intelligence (AI) algorithms to read the data collected by the CCE technology
- The use of other CCE technologies for the direct visualisation of other pathologies in the small bowel or the stomach
- The use of CCE in children.

4. Report methods for assessing the outcomes arising from the use of the intervention

4.1 *Overview of systematic review methodology*

A systematic review will be conducted to identify evidence on the clinical effectiveness, diagnostic accuracy and safety of CCE using PillCam COLON 2.

Inclusion criteria

The inclusion criteria for the review will be in line with the decision problem defined in the NICE scope.[10] These are detailed in the sections below.

4.2 *Population and subgroups*

- 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 index colonoscopy.

Where evidence is available, subgroups may include:

- People with symptoms suggestive of colorectal cancer with a FIT score between 10-100µg/g
- People with symptoms suggestive of colorectal cancer with a negative FIT result of <10µg/g with concerning clinical symptoms
- People who have declined optical colonoscopy
- People who have had an incomplete optical colonoscopy despite adequate bowel preparation.

Studies with wider populations that include the target population(s) or subgroup(s) of interest, but which present data for particular population(s) or subgroup(s) of interest, will be included. Should there be insufficient evidence relating to the populations of interest, studies with populations that include more than 80% participants representing the populations of interest will be included.

As noted in Section 3.7, we anticipate that most of the available published evidence on the diagnostic accuracy of PillCam COLON 2 will relate to mixed populations of patients who have an indication for colonoscopic investigation due to a variety of reasons (people with a family history of bowel cancer, those who have tested positive at screening, those presenting with symptoms and those who are scheduled to undergo bowel surveillance). As such, it is unlikely that the published evidence will relate to symptomatic patients who have previously undergone FIT. If data from the NHS England pilot study[12] are available, these are likely to directly reflect the subgroups of symptomatic patients listed in the NICE scope.[10]

It is possible that acceptability, uptake, completion rates and patient preferences for CCE may vary according to socioeconomic and demographic factors such as ethnicity. Where available, data will be extracted and reported separately for these subgroups.

4.3 *Interventions*

One intervention will be included in the review - PillCam COLON 2.

4.4 *Comparators*

Two potential comparators will be included in the review: (i) optical colonoscopy and (ii) CTC.

For diagnostic accuracy studies, colonoscopy is considered the gold standard. Other reference standards will be considered where data using the preferred reference standard are unavailable.

4.5 *Outcomes*

Relevant outcomes include 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:
    - 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.

Clinical outcomes:

- 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 AEs associated with CCE, colonoscopy and CTC
- Mortality.

Patient-reported outcomes:

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

We anticipate that there will not be any published evidence for the use of CCE on several of these outcomes and some outcomes may not be available from the NHS England pilot study. In such instances, where possible, the outcomes will be predicted by the economic model based on a combination of other evidence and assumptions.

4.6 *Types of clinical evidence required and study designs*

For the review of diagnostic test accuracy, only cohort studies that recruited patients regardless of diagnosis will be included (i.e., studies that avoided a case-control design).

For the review of clinical effectiveness, randomised controlled trials (RCTs) will initially be sought. If there is insufficient evidence from RCTs, non-randomised controlled trials will be sought.

Relevant systematic reviews identified during study selection will be used to check for additional studies, and used for data extraction, where relevant.

Studies will be restricted to full-text, English-language articles. If insufficient data are available, published abstracts will be considered for inclusion if they provide relevant outcome data and sufficient methodological details are reported to allow critical appraisal of the study quality.

4.7 *Exclusion criteria*

Population:

- Children
- Asymptomatic patients (referred from the screening programme)
- 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.

4.8 *Search strategy*

The search strategy for the systematic review will comprise the following main elements:

- Searching of electronic databases, registers and websites
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and existing systematic reviews.

The databases, trial registers and websites that will be searched include the following:

- MEDLINE and MEDLINE in Process (via Ovid)
- EMBASE (via Ovid)
- Cochrane Database of Systematic Reviews (via Wiley)
- Cochrane Central Register of Controlled Trials (via Wiley)
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA) Web of Science Citation Index Expanded (via Clarivate Analytics)
- Web of Science Conference Proceedings Citation Index (via Clarivate Analytics)
- WHO International Clinical Trials Registry Platform
- Clinicaltrials.gov
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- American Association for Cancer Research (AACR)
- European Cancer Organization (ECCO) Congress.

Search terms will include both product names and any alternative names for the intervention test, combined with search terms for the bowel. Manufacturer website publication lists will also be searched for potentially relevant studies. A draft MEDLINE search strategy is included in Appendix 9.1.

Reference lists of included papers, as well as existing systematic reviews, will be assessed for additional relevant studies. Where necessary and where time allows, authors of eligible studies will be contacted for further information. Only human studies will be eligible for inclusion. No limits relating to study design will be applied. Searches will be limited to studies published in 2009 or later (the year prior to the launch of Pillcam COLON 2).

4.9 *Study selection and data extraction strategy*

Study selection

The title and abstract of each record retrieved by the search strategy will be assessed against the inclusion criteria for the review, and irrelevant records will be excluded. A 5% sample of

the records retrieved by electronic searches will be checked by two reviewers, and if there is agreement, the rest of the records will be assessed by one reviewer. Disagreement in this sample may lead to double checking of a second 5% sample. The full text of remaining records will be obtained and assessed against the inclusion criteria. Study selection will be conducted by one reviewer. Any studies which give rise to uncertainty will be reviewed by a second reviewer with involvement of a clinical advisor when necessary.

Data extraction

A data extraction form will be constructed in Microsoft Excel. It may be necessary to use different data extraction forms for different study designs.

Data will be extracted by one reviewer and checked by a second reviewer. Any disagreements will be resolved through discussion and consultation with a clinical advisor where necessary. Data from multiple publications of the same study will be extracted as a single study. Where studies have wider populations or comparators outside the NICE scope,[10] only relevant data will be extracted.

4.10 *Quality assessment / risk of bias strategy*

Studies will be quality assessed by one reviewer and checked by a second reviewer. Any disagreements will be resolved through discussion and consultation with a clinical advisor where necessary. If sufficient evidence is found, the impact of the quality of studies on the evidence base will be evaluated through sensitivity analyses in meta-analysis, or through narrative synthesis of the results.

Studies will be assessed using quality assessment tools relevant to the study design. Tools may be adapted or abbreviated to the specifics of this review, due to time and resource constraints. For the review of clinical effectiveness, this may be the Cochrane Risk of Bias 2 tool for RCTs,[13] and the Risk of Bias in Non-Randomised Studies (ROBINS)-I tool for non-randomised clinical trials.[14] For the review of diagnostic test accuracy, the QUADAS-2 tool[15] may be used.

4.11 *Methods of analysis/synthesis*

Where sufficient data exist, pooled estimates of diagnostic parameters will be estimated using a hierarchical meta-analysis model to account for the correlation between sensitivity and specificity.[16-18] Adjustment for imperfect reference standards will also be considered. Random effects meta-analysis will be used to account for the heterogeneity between studies that is generally expected in diagnostic accuracy studies. Reasons for the heterogeneity in sensitivity and specificity between studies, according to subgroups of interest identified in Section 3.3, may be explored using meta-regression and/or subgroup analyses. Analyses will be conducted

in R[19] using a suitable Markov Chain Monte Carlo (MCMC) sampler such as JAGS[20] or WinBUGS.[21] Results will be displayed as forest plots and summary receiver operating characteristic (SROC) plots with 95% credible intervals (CrIs) and 95% prediction intervals (PrIs) for sensitivity and specificity.

Statistical synthesis of clinical outcomes will also be conducted, if appropriate.

4.12 *Methods for estimating health-related quality of life*

HRQoL estimates reported within the clinical literature, i.e., those relating to the use of CCE, colonoscopy and CTC, will be collated as part of the systematic review. Further data on HRQoL to inform the health economic modelling will be identified as part of Section 5.

5. Report methods for synthesising evidence of cost effectiveness

5.1 *Identifying and systematically reviewing published cost-effectiveness studies*

A systematic review will be undertaken to identify 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 strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers.

The databases that will be searched include the following:

- MEDLINE and MEDLINE in Process (for latest publications)
- EMBASE
- Web of Science Citation Index Expanded
- Web of Science Conference Proceedings Citation Index.

Where applicable, cost-effectiveness studies will be identified using an economic search filter. References of key studies will be checked. Studies will only be included if they address the decision problem set out in the final NICE scope.[10] Additional searches, for example, to inform the health economic model parameters, where required in the course of the assessment, will be undertaken through consultation between the SCHARR team.

5.2 *Evaluation of costs and cost effectiveness*

Only full economic evaluations published in English addressing the cost-effectiveness of PillCam COLON 2 (the second generation of the PillCam COLON 2) compared with current standard colonic imaging methods including colonoscopy and CTC, will be critically appraised using published checklists. Only studies which relate to the symptomatic secondary care population or the high-risk colorectal cancer surveillance population will be evaluated. If time permits, we will explore whether economic evaluations exist for colonoscopy or CTC in the appraisal populations. Relevant studies will be sifted by title and abstract and the data will be extracted into a separate Excel form. The quality of identified cost-effectiveness studies will be assessed against a critical appraisal checklist based on checklists reported by Drummond *et al.*[22] and Eddy *et al.*[23] (see Appendix 9.2).

5.3 *Development of a de novo health economic model*

A health economic model will be developed to assess the cost-effectiveness of PillCam COLON 2 for the investigation of people in the target populations as defined by the NICE scope[10] (see Section 3.3), compared to other imaging modalities currently used in this setting (colonoscopy and CTC).

The economic analysis will be conducted in line with the NICE Reference Case.[24] The economic analysis will adopt an NHS and PSS perspective and a lifetime perspective. Health outcomes and costs will be discounted at a rate of 3.5% per annum. The model will explicitly consider the diagnostic accuracy of PillCam COLON 2 CCE and its comparators from the data identified within the clinical review (see Section 4). Modelling assumptions and model parameter values will be taken from published literature retrieved by the review of cost-effectiveness studies and additional targeted searches where necessary. Study data, routine cost sources, and clinical expert opinion, will also be used. As noted in Section 3.7, it may be possible to use interim data from the NHS England pilot study[12] to inform some of the model parameters.

5.3.1 Model structure

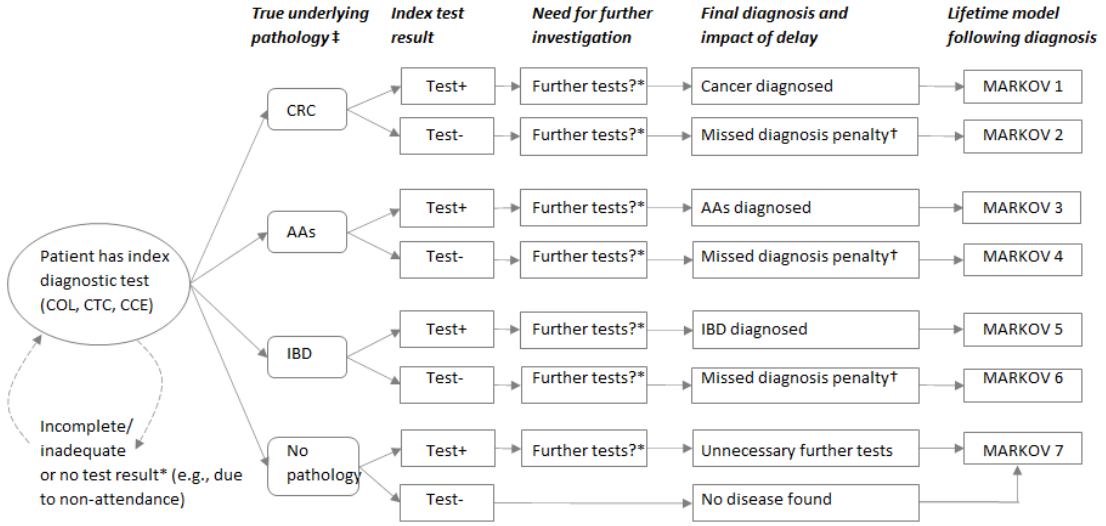
It is anticipated that the structure of the model developed for this assessment will be based on a hybrid decision tree and state transition approach which captures diagnostic pathways, progression along the adenoma-carcinoma sequence and cancer-related/other-cause mortality. The model will take account of the uptake of each test and the need for subsequent tests (e.g., following incomplete colonoscopy or a positive CCE or CTC).

The diagnostic pathways included in the model structure will be determined using clinical guidelines and through consultation with clinical experts. It is anticipated that a single economic model will be developed which will then be evaluated according to the characteristics of the population under consideration. Specifically, we anticipate that the comparator test, the suitability of subsequent diagnostic tests and additional procedures and the underlying prevalence of relevant bowel pathology will differ according to the populations and subgroups listed in Section 3.3 (i.e., whether the patient has symptoms, their FIT score, their history of prior adenomas and their ability to undergo subsequent colonoscopy if dysplasia is detected through the index test). A schematic of the general model structure is shown in Figure 1.

People who have not received a FIT due to bypass symptoms are not included in the scope of this appraisal. These patients will not be considered in the economic model. According to clinical experts invited to the scoping workshop, people with symptoms who are referred to

secondary care with a FIT score higher than 100µg/g may not be eligible to receive a CCE test due to their higher risk of CRC; these patients may be excluded from the economic model.

Figure 1: Schematic of proposed model approach



** The further tests required will depend on suitability/acceptability of colonoscopy and the pathology detected by the index test. This may include diagnostic/therapeutic colonoscopy, CTC, flexible sigmoidoscopy, or other tests*
† For patients with underlying CRC, this penalty will be estimated as a potential worsening in cancer stage. For people with AAs, a penalty will be applied to reflect an increased risk of progression to cancer. For people with IBD, a penalty will be applied to reflect potential worsening of severity at the point of later diagnosis.
‡ Prevalence of pathology will differ between the populations listed in the final NICE scope

The decision tree component of the model will have a short time horizon and will estimate the results of the index diagnostic test for each cohort of patients. The decision tree will be followed by a series of state transition models with a lifetime time horizon to estimate life years, QALYs and costs for people according to their underlying disease status at final diagnosis. All tests will be assigned a probability of test failure (e.g., incomplete colonoscopy to the caecum, inadequate bowel preparation and technical failure of CCE).

Population 1: Patients who are suitable for colonoscopy (including those who are scheduled for once-only surveillance colonoscopy)

For the population in whom colonoscopy is suitable, the current care pathways are likely to be as follows. Patients with a positive colonoscopy result for colorectal cancer (CRC) (true-positives) will receive a CRC diagnosis will be assumed to undergo a CT scan and/or magnetic resonance imaging (MRI) scan to establish the stage of the cancer (based on Dukes' CRC stage). These patients will go on to receive treatment for CRC and their survival will be modelled conditional on their age and stage at diagnosis. Advanced cancer stage will be associated with lower HRQoL and higher disease management costs. Patients with a false-negative result for CRC may be discharged and will be assumed to re-present later,

subsequently reaching a diagnosis after some diagnostic delay. During this delay period, the patient may progress to a more advanced CRC stage, leading to a comparatively worse CRC stage distribution at the point of diagnosis.

Colonoscopy can also detect polyps and other lower GI pathologies (i.e., IBD). Patients with a true-positive colonoscopy result for advanced adenomas will be assumed to receive treatment (polypectomy) and will move to the corresponding lifetime state transition model. Patients with a false-negative result for adenomas will be assumed to be diagnosed following a delay which will be associated with a higher probability of progression to CRC. Patients receiving a true-positive result for IBD will be assumed to receive the treatment for their relevant pathology (Crohn's or ulcerative colitis) and associated treatment costs. Patients with a false-negative result for IBD will be assumed to be diagnosed later with a temporary increase in disease severity, worse HRQoL and higher costs.

For patients without any underlying bowel pathology who are true-negatives, survival will be modelled using life tables and no additional costs will be included. Patients with a false-positive result may undergo additional unnecessary tests before a correct diagnosis is achieved, thereby incurring additional costs.

Within this population, CCE may be used as a triage-test to determine whether the patient needs to go on to receive a colonoscopy (including either biopsy or polypectomy).

Population 2: Patients who are unsuitable for or unwilling to undergo colonoscopy
For people in whom colonoscopy is not suitable (e.g., due to frailty or other contraindications or incomplete colonoscopy despite adequate bowel preparation) or for people who are unwilling to undergo colonoscopy, the relevant comparator test is most likely to be CTC. The model will follow the logic described above.

Within this population, CCE may be used to directly replace CTC. We anticipate that the subsequent diagnostic pathways for CCE and CTC will be the same as each other, as both technologies are non-invasive visualisation approaches.

Across both populations, the model is anticipated to include costs associated with: (i) the use of imaging tests in secondary care (PillCam COLON 2, colonoscopy and CTC); (ii) clinical appointments and other resource use related to secondary care referrals; (iii) the management of AEs associated with colonoscopy, CTC and PillCam COLON 2; (iv) the management of further diagnostic work up, including those associated with incorrect test results and

inappropriate follow-on tests; (v) resource use related to staging CRC; and (iv) lifetime treatment costs for CRC (by stage and age at diagnosis) and other non-malignant pathologies (polyps and IBD).

Resource costs associated with PillCam COLON 2 will include: cost of the device, including consumables, associated with the accompanying software system, maintenance, and service costs, and costs of staff and associated training, the appointment at which the capsule is swallowed, the use of patency capsules and costs of repeat/follow up tests.

Resource costs will be valued using unit costs obtained from routine costing sources (e.g., NHS Reference Costs,[25] the Personal Social Services Research Unit (PSSRU),[26] the British National Formulary (BNF)[27]), existing studies retrieved from targeted reviews, the technology manufacturer's submission, and through personal communication with clinical experts.

Utility values will be applied to each of the model health states and will be based on literature and/or other available sources. Utility decrements related to AEs associated with colonoscopy, CTC and CCE, and patient-reported outcomes for anxiety associated with testing, waiting for results and further diagnostic workup will be considered for inclusion if evidence allows. Within the model, QALYs will be calculated by multiplying the time spent in each health state by its associated utility value and through QALY losses associated with complications. Utility values will be age-adjusted using EQ-5D-3L estimates reported by Hernández Alava *et al.*[28]

Colonoscopy capacity constraints will be accounted for in two ways: (i) through the negative direct health impact associated with delays in reaching a diagnosis, and (ii) through the estimation of reductions in the need for specific investigations such as colonoscopy and the time spent waiting for these investigations. This approach is similar to that used in the model developed to inform NICE Diagnostics Guidance 56. If possible, we will attempt to estimate quantitative benefits of released endoscopy capacity based on other models or analyses that have been undertaken.

5.3.2 Model analyses

Cost-effectiveness will be expressed in terms of the incremental cost per QALY gained. Net health benefit (NHB) will be used when comparing multiple treatment options. Costs will be valued at current prices.

Deterministic sensitivity analysis (DSAs) will be undertaken to explore the sensitivity of the results to variations in specific input parameters. Scenario analyses will be presented to explore

the impact of alternative assumptions and evidence sources. Results will be presented for important subgroups for which sufficient evidence exists. Probabilistic sensitivity analysis (PSA) will be undertaken using Monte Carlo sampling. The uncertainty around each parameter will be represented using a probability distribution, with correlation between parameters maintained if identified. Decision uncertainty will be presented using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

A number of approaches will be used to ensure the credibility of the health economic model, including:

- Ensuring that the model is consistent with the NICE Reference Case[24] and published checklists for economic evaluations/models.[22, 29]
- Double-programming the deterministic version of the model by the model author.
- Checking model implementation by a third-party modeller who is not involved in developing the model itself.
- Ensuring the accuracy of model input parameters against their original sources.
- Checking the appropriateness of model input parameters and assumptions with clinical experts.
- Checking the face validity of the model predictions with clinical experts.

6. Handling information from the companies

All data submitted by the manufacturer will be considered if received by the EAG no later than Thursday 5th October 2023. Data arriving after this date may not be considered.

If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any 'academic in confidence' data provided by the manufacturer, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any personal data received will be highlighted in pink and underlined. Any confidential data used in the cost-effectiveness model will also be highlighted.

A version of the economic model with confidential information redacted or replaced with dummy data will be provided.

7. Competing interests of authors

None

8. Timetable/milestones

Milestone	Date to be completed
Final date for manufacturer/sponsor data submissions	05/10/2023
Progress report	01/12/2023
Draft EAG report	19/02/2024
Final EAG report to NICE	18/03/2024

9. Appendices

9.1 Draft search strategy

Ovid MEDLINE(R) ALL <1946 to September 01, 2023>

1 exp Colon/ 75082
2 (colon* or colo* or rectum or rectal or bowel*).mp. 1502727
3 1 or 2 1502727
4 Capsule Endoscopy/ 3566
5 capsule endoscop*.mp. 5977
6 (pillcam or pill-cam).mp. 286
7 CCE.mp. 1835
8 4 or 5 or 6 or 7 7651
9 exp Colorectal Neoplasms/ 238709
10 (cancer* or tumo* or neoplasm* or adenoma* or carcinoma* or polyp*).mp. 5050272
11 9 or 10 5050366
12 3 and 8 and 11 1431
13 limit 12 to yr="2009 -Current" 1111

9.2 Critical appraisal checklist for economic evaluations using key components of the British Medical Journal checklist for economic evaluations (Drummond *et al*) together with the Eddy checklist on mathematical models employed in technology assessments (Eddy 1985)

Reference ID		
Title		
Authors		
Year		
Modelling assessments should include:		**Yes/No**
1	A statement of the problem;	
2	A discussion of the need for modelling vs. alternative methodologies	
3	A description of the relevant factors and outcomes;	
4	A description of the model including reasons for this type of model and a specification of the scope including; time frame, perspective, comparators and setting. *Note: n=number of health states within sub-model*	
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence;	
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships, and distributions) and the data;	
7	A list of parameter values that will be used for a base case analysis, and a list of the ranges in those values that represent appropriate confidence limits and that will be used in a sensitivity analysis;	
8	The results derived from applying the model for the base case;	
9	The results of the sensitivity analyses; unidimensional; best/worst case; multidimensional (Monte Carlo/parametric); threshold.	
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect;	
11	A description of the validation undertaken including; concurrence of experts; internal consistency; external consistency; predictive validity.	
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results;	
13	A description of research in progress that could yield new data that could alter the results of the analysis	

10. Additional information that is needed by NETSCC, HTA and NICE. Please send this as a WORD document when you submit your protocol to [redacted]

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Timetable/milestones

- Progress report (to NETSCC, HTA who forward it to NICE within 24 hrs): 01/12/2023
- Assessment report (simultaneously to NICE and NETSCC, HTA): 18/03/2024

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