**Draft Protocol for Evidence Assessment and Analysis Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence**

HTA Reference 15/17/05

25th February 2016

## 1. Title of the project

Virtual chromoendoscopy for the real-time assessment of colorectal polyps in vivo

## 2. Name of External Assessment Group (EAG) and project lead

Dr Jonathan Shepherd
Principal Research Fellow
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
1st Floor, Epsilon House, Enterprise Road
Southampton Science Park, Southampton, SO16 7NS
Tel: +44 (0) 2380 597055
Email: jps@southampton.ac.uk
Website: www.southampton.ac.uk/shtac

Other members of the team:
Dr Keith Cooper, Senior Research Fellow (Health economics)
Dr Jo Picot, Senior Research Fellow
Dr Karen Pickett, Research Fellow
Mr Micah Rose, Research Fellow (Health economics)
Mrs Karen Welch, Information Specialist

## 3. Plain English Summary

Colorectal polyps are growths that can develop in the large bowel. Around one in five people in the UK get bowel polyps. Most are not cancerous, but some types, called adenomas, can

become cancerous if not diagnosed and removed. Larger polyps are more likely to be adenomas than smaller ones. Currently, specialised doctors or nurses, called 'endoscopists', use colonoscopy to detect polyps. The endoscopist inserts a flexible tube with a camera on it into the bowel. If a polyp is found, it is removed and sent to a laboratory to examine if it is an adenoma. In some patients, polyp removal can cause bleeding or a bowel perforation (a hole in the bowel). Some patients also experience anxiety waiting for the laboratory result.

New colonoscopy techniques, called virtual chromoendoscopy, have been developed for diagnosing polyps. Endoscopists can use these techniques, along with white light, dyes and their understanding of the bowel structure, to decide in real-time which polyps are adenomas. This is called "optical diagnosis". Endoscopists could use optical diagnosis to assess very small polyps (those 5 mm or smaller), without sending them to a laboratory. The endoscopist could then decide whether to remove the polyp or, if confident that it is not an adenoma, leave it in the colon. This could reduce risks of bleeding or bowel perforation. This strategy could also reduce patients' anxiety, as they would receive results immediately. Some patients, however, may experience anxiety knowing a polyp has been left. It may also save the NHS money through reducing laboratory costs, outpatient appointments and the colonoscopy time. There is, however, uncertainty about how effective this approach is and if it would be an effective use of NHS financial resources (that is, cost-effective).

Our aim is to examine if virtual chromoendoscopy is effective and cost-effective in diagnosing whether very small polyps are adenomas in people having a colonoscopy because they have symptoms of bowel cancer, have previously had adenomas removed, or referred from the bowel cancer screening programme because of a positive screening test. We will review all the relevant research studies conducted, using standard methods. We will examine how accurately virtual chromoendoscopy diagnoses polyps and any harmful effects. In addition we will examine its impact on colonoscopy time, outpatient appointments, patients' quality of life and anxiety, and bowel cancer development. We will also review studies of the costs and consequences of using virtual chromoendoscopy. We will then develop an economic model to evaluate the benefits to patients and the NHS.

## 4. Decision problem

### *4.1. Purpose of the decision to be made*

Colorectal polyps are small growths (usually less than 1cm in size) on the inner lining of the colon or rectum.[1] They are common, affecting 15-20% of the population and they usually occur in people who are over 60 years of age.[1] Colorectal polyps don't usually cause symptoms and are not normally cancerous, however, some polyps (known as adenomatous polyps, adenomas or, less commonly, neoplastic polyps) may eventually become cancerous if undiagnosed and untreated.

Current clinical practice is to detect polyps using conventional white light endoscopy which may sometimes be used in combination with dyes (chromoendoscopy) to enhance visualisation of tissues in the area being inspected. Virtual chromoendoscopy technologies provide enhanced visualisation of tissues without necessarily the need for dyes, enabling differentiation between adenomatous and hyperplastic (non-neoplastic) colorectal polyps in real-time during colonoscopy. A range of technologies are available, classified as optical or digital chromoendoscopy. Optical technologies include narrow band imaging (NBI), and digital technologies include Flexible Spectral Imaging Colour Enhancement (FICE), and i-scan imaging. Under current clinical practice a diminutive polyp (1-5 mm in size) identified by conventional white light endoscopy would be removed and sent for histopathological examination to determine colorectal cancer risk. Use of a virtual chromoendoscopy technology would provide the endoscopist with enhanced visualisation to differentiate between adenomatous polyps (adenomas) which could be resected and discarded (i.e. not sent for histopathological assessment), and hyperplastic polyps in the recto-sigmoid area of the colon which could be left in situ. This can only be done when the endoscopist is highly confident in their characterisation of the polyp. A surveillance interval would then be set according to the number and size of adenomas detected.

The potential benefits would be fewer resections (polypectomy) of low risk hyperplastic polyps (with a resulting reduction in complications such as bleeding or perforation of the bowel); the provision of quicker results and management (including surveillance) decisions, thus reducing patient anxiety; and a reduction in health resource use through fewer histopathological examinations. Guidelines recommend virtual chromoendoscopy should be performed only under strictly controlled conditions by experienced endoscopists adequately trained in the use of the technology, using validated classification scales.[2]

In order for virtual chromoendoscopy techniques to be incorporated into routine clinical practice for the real-time assessment of colorectal polyps during colonoscopy, there needs to

be evidence that the new technology provides an appropriate and efficient standard of care compared to existing practice. Therefore, the decision question for this assessment is does virtual chromoendoscopy for real-time assessment of diminutive colorectal polyps during colonoscopy represent a cost-effective use of NHS resources?

### *4.2. Objectives*

The aim of this research is to assess the clinical-effectiveness and cost-effectiveness of technologies that could aid the characterisation of diminutive colorectal polyps that have the potential to become cancerous.

Specific objectives are to determine, through a systematic review and economic evaluation, the clinical-effectiveness and cost-effectiveness of the virtual chromoendoscopy technologies NBI, FICE, and i-scan in the characterisation and management of diminutive colorectal polyps.

### *4.3. Clear definition of the intervention*

A number of virtual chromoendoscopy technologies are available to perform real-time assessment of colorectal polyps during colonoscopy. All rely on an endoscopy system typically consisting of an endoscope (a long, flexible tube), a light source, a video processor and a visual display monitor.[3, 4] The light source produces light that is transmitted to the distal end of the endoscope to illuminate the area under inspection. The video processor captures and processes electrical signals to enable an image of the inspected area to be displayed on the monitor.[4]

Current clinical practice is to detect polyps using conventional white light endoscopy which may sometimes be used in combination with dyes (chromoendoscopy) to enhance visualisation of tissues in the area being inspected. All detected polyps are then removed and each polyp is sent for histopathological examination to determine whether it is an adenoma (therefore at a high cancer risk) or hyperplastic (therefore at a low cancer risk).[1]

The aim of virtual chromoendoscopy technologies is to provide enhanced visualisation of tissues (without the need for dyes) enabling the clinician to differentiate between adenomatous and hyperplastic colorectal polyps in real-time during colonoscopy. In optical chromoendoscopy optical lenses are integrated into the endoscope's light source, which selectively filter white light resulting in narrow band light. In contrast, in digital

chromoendoscopy digital post-processing by the video processor is used to enhance the real-time image.[5]

There are three commercial systems of relevance to this diagnostic assessment:

- Narrow band imaging (NBI), a type of optical chromoendoscopy
- Flexible Spectral Imaging Colour Enhancement (FICE), a type of digital chromoendoscopy
- i-scan, a type of digital chromoendoscopy

Each of these will be described in turn.

**Narrow band imaging (NBI)**

Narrow band imaging (Olympus Medical Systems) is an optical image enhancement technology used in the Olympus endoscopic video imaging systems EVIS LUCERA ELITE,[6] EVIS EXERA III[7] (not available in the UK) and EVIS LUCERA SPECTRUM.[8] NBI is achieved by using a filter in the light source unit and a function on the video processor. The white light is filtered resulting in narrow-band light which consists of two wavelengths 415 nm blue light and 540 nm green light.[5, 8] These wavelengths are strongly absorbed by haemoglobin and thus NBI enhances the contrast between blood vessels and the surrounding mucosa in comparison to illumination by standard white light. The image quality achieved varies between the different endoscopy systems due to differences in image sensors and video processors with the newer EVIS LUCERA ELITE system offering the highest quality images. Furthermore, within a class of endoscopy system there will also be differences depending on the precise model of endoscope used. For example, within the EVIS LUCERA ELITE group the EVIS LUCERA ELITE 290HQ (high definition) endoscope offers the highest image quality, followed by the EVIS LUCERA ELITE 290H endoscope. The endoscopist can switch viewing mode from standard white light to NBI and vice versa at any time.

**Flexible Spectral Imaging Colour Enhancement (FICE)**

FICE (Aquilant Endoscopy/FujiFilm) is a digital image processing function used in the Fuji video endoscopy systems EPX-4450HD, EPX-3500HD and EPX-4400.[9] Standard white light illuminates the area of interest and the conventional images captured from the reflected light can be processed in real-time by software into spectral images (images composed from rays having specific wavelengths). FICE has ten pre-set wavelength settings which can also be manually altered to achieve the best enhancement of the image.[5, 9] The endoscopist can

switch between viewing conventional or FICE images at any time. The image quality achieved varies between the different systems being higher on the EPX-4450HD and EPX-3500HD systems than on the EPX-4400 system. As well as being a feature of three Fuji endoscopy systems the 500 series and 600 series endoscopes can also use FICE and it can be used in combination with magnifying endoscopes.

**I-scan**

I-scan (Pentax Medical) is a digital image processing technology used with Pentax endoscopy systems.[10] Standard white light illuminates the area of interest and there are three different algorithms for real-time image processing:[5, 11]

- Surface enhancement - helps to visualise the edges of anatomical structures by improving light-dark contrast.
- Contrast enhancement - helps to visualise depressed areas by digitally adding blue colour to relatively dark areas.
- Tone enhancement - modifies the colour contrast of the normal image to create an improved image with enhanced visibility of minute mucosal structures and subtle changes in colour.

The three different algorithms are then used in different combinations for three i-scan modes: (i) i-scan 1 for detection of lesions; (ii) i-scan 2 for characterisation of lesions; (iii) i-scan 3 for demarcation of lesions. The endoscopist can switch between the conventional image and the three i-scan modes at any time. If using the appropriate equipment (the EPK-i7000) it is possible to display a normal white light image and an i-scan image simultaneously side by side.[11]

Polyps can be described in a variety of ways e.g. by size, according to the type of cell or tissue they arise from within the colon or rectum, according to their shape, or according to whether they are adenomas or hyperplastic polyps.[12] The Association of Coloproctology of Great Britain and Ireland (ACPGBI)[13] recommends the Paris endoscopic classification (which describes polyps on the basis of their morphology), in conjunction with an estimation of the size of a polyp for the prediction of malignancy (Table 1).

There are also several different classification schemes available for the virtual chromoendoscopy technologies. Each scheme is specific to a particular technology. Examples of classification schemes are shown in Table 2.

**Table 1: The Paris endoscopic classification[13-15]**

| | | |
|---|---|---|
| Protruded | Type 0-1p | Pedunculated (on a stalk) |
| | Type 0-1sp | Sub pedunculated |
| | Type 0-1s | Sessile |
| Superficial Elevated | Type 0-2a | Flat elevated |
| | Type 0-2a+2c | |
| | Type 0-2a+Depression | |
| Flat | Type 0-2b | Flat |
| Depressed | Type 0-2c | Slightly depressed |
| | Type 0-2c+2a | |
| Excavated (ulcer) | Type 0-3 | |

**Table 2: Examples of virtual chromoendoscopy classification schemes for colorectal polyps**

| **Name of Scheme** | **Basis for classification** | **Classification categories** | | |
|---|---|---|---|---|
| NBI International Colorectal Endoscopic (NICE) classification[16] | Polyp histology (based on colour, vessels and surface pattern when viewed by NBI) | Type 1 | | Hyperplastic |
| | | Type 2 | | Adenoma |
| | | Type 3 | | Deep submucosal invasive cancer |
| Kudo classification[17] | Pit pattern (fine surface structure of the of the mucosa when viewed by magnifying chromoendoscopy) | Round pits | Type 1 | Benign changes (e.g. normal, hyperplastic, inflammatory polyps) |
| | | Stellar or papillary pits | Type II | |
| | | Large tubular or roundish pits | Type III L | Neoplastic and malignant changes |
| | | Small tubular or roundish pits | Type III s | |
| | | Branch-like or | Type IV | |

| | | | | |
|---|---|---|---|---|
| | | gyrus-like pits | | |
| | | Non-structural pits | Type V | |
| Showa classification[18] | Vascular pattern (pattern of microvessels surrounding the pit when viewed by NBI) | Normal | Characteristic of non-neoplasia | |
| | | Faint | | |
| | | Network | Seen in neoplasia | |
| | | Dense | | |
| | | Irregular | Seen in neoplasia, useful for a diagnosis of cancer | |
| | | Sparse | | |

### *4.4. Populations and relevant subgroups*

The population of interest to this assessment is patients undergoing colonoscopy found to have diminutive (1-5 mm in size) colorectal polyps who were either referred for colonoscopy by a GP because of symptoms suggestive of colorectal cancer, who were offered colonoscopic surveillance because they had had adenomas previously removed or who were referred through the NHS bowel cancer screening programme.

### *4.5. Place of the intervention in the treatment pathway(s)*

Virtual chromoendoscopy takes place at the same point in the treatment pathway as current clinical practice using conventional white light endoscopy or conventional chromoendoscopy. The setting in which virtual chromoendoscopy is used is secondary or tertiary care. It is likely that virtual chromoendoscopy technologies would be used alongside standard white light endoscopy since all the technologies relevant to this assessment allow the endoscopist to change viewing mode from standard white light to the virtual chromoendoscopy image in real-time at the flick of a switch. Where the treatment pathways would diverge is when a diminutive polyp of ≤ 5mm is discovered. Under current clinical practice a diminutive (1-5 mm) polyp identified by conventional white light endoscopy would be removed and sent for histopathological examination to determine whether it is adenomatous (adenoma) or hyperplastic.[2] However, use of a virtual chromoendoscopy technology would enable the endoscopist to differentiate between adenomas and hyperplastic polyps during colonoscopy. Where the endoscopist has high confidence in the polyp characterisation, adenomas would be

removed and discarded whereas hyperplastic polyps in the recto-sigmoid area would be left in situ. This is referred to as the DISCARD strategy (Detect, InSpect, ChAracterise, Resect and Discard).[19] Where there is low confidence in determining whether a polyp is adenomatous or hyperplastic it should be resected and sent for histopathological examination. Any flat depressed polyps, polyps with a distorted shape, and hyperplastic appearing (serrated-appearing) polyps in the proximal colon should be sent for histopathology examination, irrespective of size.

There are several different aspects to any decision to implement the new technology and European[2] and American guidance[20] has been published. The European guidance,[2] produced by the European Society of Gastrointestinal Endoscopy (ESGE) in 2014 makes the recommendation that virtual chromoendoscopy (NBI, FICE, i-scan) and conventional chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive (≤5mm) colorectal polyps to replace histopathological diagnosis. The optical diagnosis has to be reported using validated scales, must be adequately photodocumented, and can be performed only by experienced endoscopists who are adequately trained and audited (weak recommendation, high quality evidence).

The American guidance[20] on real-time endoscopic assessment of the histology of diminutive colorectal polyps is part of the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) initiative of the American Society for Gastrointestinal Endoscopy. Two statements are made regarding the real-time endoscopic assessment of the histology of diminutive colorectal polyps:

1. In order for colorectal polyps ≤5 mm in size to be resected and discarded without pathologic assessment, endoscopic technology (when used with high confidence) used to determine histology of polyps ≤5 mm in size, when combined with the histopathologic assessment of polyps >5 mm in size, should provide a ≥90% agreement in assignment of post-polypectomy surveillance intervals when compared to decisions based on pathology assessment of all identified polyps.
2. In order for a technology to be used to guide the decision to leave suspected recto-sigmoid hyperplastic polyps ≤5 mm in size in place (without resection), the technology should provide ≥90% negative predictive value (when used with high confidence) for adenomatous histology.

The clinician is required to judge whether the histology of a given polyp can be assessed accurately using an endoscopic technology. If it is judged that the polyp cannot be confidently assessed using an endoscopic technology then it should be resected and sent for histopathological diagnosis. The guidance also indicates that polyp images should be stored permanently and should be of sufficient resolution to support the endoscopists' assessment and clinical decisions.

### *4.6. Relevant comparators*

The relevant comparator for virtual chromoendoscopy is removal and histopathological assessment of all diminutive (1-5 mm) polyps.

### *4.7. Current evidence base*

A number of studies have assessed the diagnostic accuracy of virtual chromoendoscopy compared with histopathological examination for differentiating neoplastic from non-neoplastic polyps during colonoscopy. The DISCARD trial (a prospective cohort study),[21] for example, found that high definition white light colonoscopy followed by non-magnified NBI accurately diagnosed whether small (6mm to <10 mm) polyps were adenomas or hyperplastic polyps, in patients who had positive faecal occult blood tests as a part of the national bowel-cancer screening programme or who were undergoing surveillance colonoscopy. It also had a 98% agreement with histological examination for assigning surveillance intervals, based on British Society for Gastroenterology guidelines. The authors concluded that it is feasible to incorporate optical diagnosis technologies into clinical practice for the identification of small (< 10 mm) polyps.

We have identified four published systematic reviews which have compared the diagnostic accuracy of virtual chromoendoscopy technologies with histopathological examination for differentiating neoplastic from non-neoplastic polyps during colonoscopy.[22-25] Two reviews focused solely on studies of NBI,[23, 25] while the other two included studies of a range of virtual chromoendoscopy technologies, including NBI, i-scan and FICE.[22, 24] The reviews incorporated studies with a variety of designs; none were limited to RCTs. All the reviews conducted meta-analyses and assessed diagnostic accuracy outcomes, including sensitivity, specificity, negative predictive value (NPV), the summary receiver operating characteristic (SROC) curve, and the area under the SROC curve. The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee conducted a review that specifically included studies assessing the NPV of optical biopsy for assessing the histology

of small and diminutive polyps.[24] The review examined whether NBI, i-scan and FICE met the PIVI performance thresholds and therefore whether or not the evidence supported a "diagnosis-and-leave" (ASGE Technology Committee, 2015, p. 1) approach.[24] In the reviews, a range of subgroup analyses were conducted, including of diminutive polyps,[22, 23] high confidence predictions,[23] the type of NBI system used (e.g. Lucera or Exera),[23] study quality[23] and operator experience.[24] The authors of these reviews have concluded that these endoscopic imaging technologies result in reliable diagnosis of neoplastic lesions, including neoplastic diminutive polyps, during colonoscopy[22,23, 25] and show potential for use in practice.[22, 23] The ASGE Technology Committee review assessing the techniques against the PIVI criteria concluded that only NBI met the criteria for implementation in practice, when it was used by an expert endoscopist and for high confidence assessments.[24]

Our proposed systematic review will include a narrower range of studies than the previous reviews by focusing only on those evaluating diminutive polyps and only studies of virtual chromoendoscopy used in real time (see Section 5.1). In addition to assessing diagnostic accuracy, the review will aim to include, where data are available, outcomes not considered in the previous reviews, including the time it takes to carry out the colonoscopy, health-related quality of life, adverse effects of polypectomy, occurrence of colorectal cancer and mortality (see Section 5.4).

## 5. Report methods for assessing the outcomes arising from the use of the interventions

This section reports the scope and methods for the systematic review of clinical-effectiveness in this assessment.

### *5.1. Population*

The target population for virtual chromoendoscopy in this assessment is:

- People with symptoms that may be suggestive of colorectal cancer who are referred for colonoscopy by a GP
- People offered colonoscopic surveillance because they have had adenomas removed
- People referred for colonoscopy following bowel cancer screening

The target population does not include people undergoing monitoring for inflammatory bowel disease (e.g. Crohn's disease); and people with polyposis syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer), or familial adenomatous polyposis.

### *5.2. Interventions*

- Narrow Band Imaging - EVIS LUCERA ELITE, EVIS LUCERA SPECTRUM and EVIS EXERA (Olympus Medical Systems) (NB. The EXERA system is not available in the UK but expert advice is that diagnostic outcomes are similar to the EVIS LUCERA series).
- FICE (Fujinon/Aquilant Endoscopy)
- I-scan (Pentax Medical)

Studies of the above technologies will only be included when used with high definition or high resolution endoscopy systems, without the use of magnification. Studies will only be included when the technologies are used in real-time for diagnosis (as opposed to post-procedure image-based diagnosis).

Where data allow outcomes will be assessed in relation to the following factors:

- Level of expertise and experience in optical assessment of polyps of the endoscopist
- Level of confidence in polyp assessment
- Location of polyp
- Use of different polyp classification criteria

### *5.3. Comparators (reference standard)*

Histopathological assessment of resected diminutive (1-5 mm) colorectal polyps.

### *5.4. Outcomes*

The following outcomes will be included, where reported.

Intermediate measures for consideration may include:

- Accuracy of virtual chromoendoscopy characterisation of polyp (e.g. adenoma, hyperplastic)
- Number of polyps designated to be left in place
- Number of polyps designated to be resected and discarded

- Number of polyps designated to be resected and sent for histopathological examination
- Recommended surveillance interval
- Length of time to perform the colonoscopy
- Number of outpatient appointments or telephone consultations

Patient-reported outcomes for consideration may include:

- Health related quality of life (HRQoL) including anxiety

Clinical outcomes for consideration may include:

- Adverse effects of polypectomy
- Colorectal cancer
- Mortality

### *5.5. Study design*

Studies will be eligible for inclusion if they are experimental or observational in which the intervention(s) of interest (i.e. NBI, FICE and/or i-scan) have been used in people to predict polyp histopathology and this has been followed by histopathological assessment of the excised polyps. Studies must report at least one of the clinical outcomes of relevance to this assessment (e.g. Accuracy of virtual chromoendoscopy for polyp characterisation, recommended surveillance interval, HRQoL, colorectal cancer). Only studies evaluating diminutive polyps (1-5 mm in size) will be included. Studies of larger sized polyps will be eligible if outcome data are given for the sub-group of diminutive polyps. Studies such as editorials and case-reports will not be included. Systematic reviews will be used as a source of references.

### *5.6. Search strategy*

A comprehensive search strategy will be developed, tested and refined by an experienced information specialist (see Appendix 1 for a draft Medline search strategy). The search strategy will aim to identify studies of the diagnostic accuracy of virtual chromoendoscopy and studies providing relevant clinical outcomes (morbidity, mortality, HRQoL) using the interventions and relevant comparator as specified above.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field

- Scrutiny of bibliographies of included studies

Electronic resources to be searched will include:

- General health and biomedical databases – MEDLINE (Ovid); PreMedline In-Process & Other Non-Indexed Citations; EMBASE; the Cochrane Library; Web of Science; Database of Abstracts of Reviews of Effectiveness (DARE); Health Technology Assessment database; MEDION database of diagnostic accuracy studies.
- Relevant conferences, for example: the Association of Coloproctology of Great Britain and Ireland Annual Meeting; the Annual Meeting of the European Society of Coloproctology; the American Society for Gastrointestinal Endoscopy (ASGE) Digestive Disease conference; Digestive Disease Week conference; the United European Gastroenterology (UEG) Week conference.
- Internet pages of relevant institutions and other organisations such as the British Society of Gastroenterology, the European Society of Gastrointestinal Endoscopy, the American Society for Gastrointestinal Endoscopy, and the American Gastroenterological Association.
- Grey literature and research in progress – UK Clinical Research Network Portfolio Database; World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); ISRCTN (controlled and other trials); Clinical Trials.gov; NIHR Clinical Research Network Portfolio; UK Clinical Trials Gateway (UKCTG).

All databases will be searched from database inception to the present and searches will be limited to the English language. Systematic reviews will only be retrieved in order to check their reference lists for potentially relevant primary research studies.

Studies published as abstracts or conference proceedings will be included only if published in 2014, 2015 or 2016 and if sufficient details are presented to allow appraisal of the methodology and the assessment of results to be undertaken.

For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required (see Section 6) and will include a wider range of study types such as economic evaluations.

### *5.7. Data extraction strategy*

Studies will be selected for inclusion through a two-stage process using the predefined and explicit criteria specified above. The titles and abstracts of bibliographic records identified by the search strategy will be assessed by two reviewers independently for potential eligibility. Full papers of studies which appear potentially relevant will be requested for further assessment. These will be screened by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. At both stages any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

Relevant data will be extracted on the study and population characteristics, methodological details of the technologies under comparison and diagnostic outcomes. Where reported, data on morbidity, mortality and HRQoL will also be extracted. Data extraction and quality assessment will be undertaken by one reviewer and checked by a second reviewer using a pre-designed and piloted data extraction form (see Appendix 2) to avoid any errors. Any disagreements between reviewers at the study selection and data extraction stages will be resolved by consensus or if necessary by arbitration by a third reviewer. Papers that refer to the same primary study will be assessed together, to avoid double-counting of information.

### *5.8. Quality assessment strategy*

The methodological quality of studies will be assessed by one reviewer and checked by a second reviewer, with any disagreements resolved by consensus or if necessary by arbitration by a third reviewer. The quality of studies reporting diagnostic accuracy will be assessed using the Cochrane Collaboration adaptation[26] of the QUADAS tool (Quality Assessment Tool for Diagnostic Accuracy Studies)[27] which can be used to assess a variety of study designs (e.g. RCT, non-RCT, prospective cohort studies).

### *5.9. Methods of analysis/synthesis*

Studies will be synthesized through a structured narrative review with tabulation of results of included studies. Where appropriate and where suitable data are available, meta-analysis will be employed to synthesise data on test sensitivity and specificity. The appropriateness of meta-analysis will be determined by assessing the clinical heterogeneity of the included studies. Any meta-analysis conducted will be informed by critical appraisal of the included studies during the quality assessment step (e.g. sensitivity analyses may be conducted to assess the effect of study quality on diagnostic outcomes). Where possible, the analysis and synthesis will follow good practice approaches as recommended by the Centre for Reviews

and Dissemination (CRD) (Chapter 2: Systematic reviews of Clinical Tests),[28] the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,[29, 30] and the NICE Diagnostics Assessment Programme Manual.[31]

## 6. Report methods for synthesising evidence of cost effectiveness

### *6.1. Identifying and systematically reviewing published cost-effectiveness studies*

A systematic review will be conducted of published economic evaluations according to the methods detailed in Section 5. The population, interventions and comparators included will be the same as for the systematic review of clinical effectiveness (as described in Section 5) with the exception of the study design and outcomes. In terms of design, studies will be included if they are full economic evaluations, assessing costs and consequences, of the specified virtual chromoendoscopy technologies. Relevant outcomes include life years, incidence of colorectal cancer or Quality Adjusted Life Years (QALYs). Data from the full economic evaluations meeting the inclusion criteria will be extracted into structured tables using standardised forms by one health economist and checked by a second health economist. The quality of the included studies will be assessed using a critical appraisal checklist based upon that proposed by Drummond and colleagues[32] and Philips and colleagues.[33] The results of the studies will be discussed in a narrative review. The review will assess whether any of the studies identified would provide an appropriate structure (with or without modification) to inform economic modelling in this assessment.

### *6.2. Evaluation of costs and cost effectiveness*

Decision analytical economic modelling will be undertaken to determine the cost-effectiveness of virtual chromoendoscopy technologies for real-time assessment of diminutive colorectal polyps. The model used in the assessment will be constructed according to standard modelling guidelines and a full explanation of our methods for formulating model structure and deriving parameter values will be given in the assessment report. The perspective of the analysis will be the NHS and Personal Social Services (PSS). Both costs and benefits will be discounted at 3.5% per annum. The results will be reported as cost per QALY gained, where possible.

The modelled population will be as specified in Section 5.1 (i.e. people with symptoms suggestive of colorectal cancer referred for colonoscopy by a GP; people offered colonoscopic surveillance because they have had adenomas removed; and people referred for

colonoscopy following bowel screening). The model will include the costs associated with virtual chromoendoscopy including endoscopy system costs, training costs, colonoscopy and histopathology costs and costs of treating subsequent colorectal cancer. Cost data will be collected from routine sources (e.g. NHS reference costs; the Personal Social Services Research Unit; and the manufacturers of the endoscopy systems), and, where available, from primary data from published studies.

Model parameter values, such as diagnostic sensitivity and specificity of the technologies, transition rates between health states, HRQoL, adverse event rates and costs, will be obtained from our clinical and cost-effectiveness systematic review and targeted literature searches. The model will be validated by checking its structure, calculations and data inputs for technical correctness. The model structure and any assumptions made will be verified by clinical experts for appropriateness of clinical and diagnostic pathways.

Model uncertainty will be explored through one-way sensitivity analyses for all key parameters, scenario analyses, and probabilistic sensitivity analyses where possible. These analyses will include variables for diagnostic accuracy, and the frequency and characteristics of polyps resected and discarded. Where data allow, scenario analyses will be conducted for factors that may affect cost-effectiveness, such as endoscopist expertise, polyp location and the use of different polyp classification criteria.

### *6.3. Development of the health economic model*

The structure of the model will be informed by the systematic review of cost-effectiveness, expert opinion, clinical guidelines, and any additional relevant models identified from the literature. Our preliminary searches have identified two full economic evaluations that are within the scope of this assessment (Hassan and colleagues[34] and McGill and colleagues[35]). Both studies evaluated the cost-effectiveness of a resect and discard policy whilst using NBI for colonoscopy screening in a US population. Both used Markov models to reflect the natural history of polyp and cancer development. However, the models reported in these evaluations did not consider the training time associated with endoscopy systems, system costs, expertise of the endoscopist or the location of polyp (although details are limited for the study by McGill as this is reported as an abstract only).

To identify other potentially relevant model structures, a wider search will be conducted among NICE technology appraisals, and models associated with national and international

guidelines and screening programmes. In our preliminary searches, the current NHS Bowel Cancer Screening Programme (NHS BCSP) model has been identified as being potentially useful for this assessment. The NHS BCSP model was published in 2012 by Whyte and colleagues[36] and has been adapted at least twice since 2012,[37, 38] with a current adaptation in process by Murphy and Gray (2015).[37]

The latest service specification for the NHS BCSP provides details on patient pathways for colonoscopy.[39, 40] This pathway has been adapted to reflect the scope of this assessment from NICE and the DISCARD strategy[19] to inform potential disease monitoring pathways in this assessment. Current guidelines from the British Society for Gastroenterology (BSG), the European Society of Gastroenterologists (ESGE), and NICE will be consulted to inform management for individual polyp types.[41-43] Clinical advisors will be consulted to address how guideline pathways can inform the economic model structure. Figure 1 provides the relevant portion of the patient pathway for surveillance and screening, based upon current guidelines, with some adaptation to represent how the economic evaluation would fit within the pathway.

The proposed model will follow a cohort of patients who have a colonoscopy, for each of the four diagnostic options: histopathology, NBI, FICE and i-scan. All elements of the model structure are subject to change based on the availability of evidence, and expert validation. In the histopathology arm, all polyps are resected but none are discarded. In all other strategies, polyps that can be optically assessed with high confidence and diagnosed as adenomas may be resected and discarded, and polyps in the recto-sigmoid area of the colon that can be optically assessed with high confidence as hyperplastic polyps will be left in situ. Polyps that cannot be optically assessed with high confidence, polyps with depressed morphology, and polyps proximal to the recto-sigmoid area will be resected and sent for histopathological assessment. If evidence allows, an analysis will be undertaken where all polyps in the rectosigmoid area are left in situ for standard assessment (histopathology) and for all virtual chromoendoscopy. This alternative analysis is based on expert commentary that polyps in the rectosigmoid area are now routinely left in situ. Patients will then be assigned a surveillance interval according to the results of the diagnostic test.

Currently, the proposed model only assesses patients with exclusively diminutive polyps. We have excluded small and large polyps because the management strategy for these polyps would be identical across all assessment strategies (resection for histopathological

assessment) which would indicate that including these polyps would increase the complexity of the model, without likely gains in information for decision making. However, we will review the feasibility of extending the model to include a mix of diminutive polyps. Current guidance pathways include patients with a mix of polyp sizes. In the NICE BCSP pathway, a patient with 3 to 4 small adenomas (diminutive are a subset) or at least one large adenoma (>10mm) are defined as intermediate risk and assigned to three yearly screening, whilst a patient with 5 or more small adenomas or three or more large adenomas are defined as high risk and assigned to a repeat colonoscopy in one year, with further surveillance intervals defined by the repeat colonoscopy. In Figure 1 and Figure 2, small and large polyps are excluded.

Figure 2 shows a simplified potential structure for the decision pathway that highlights what occurs in patients according to the number of adenomas identified. After all polyps are characterised some patients will have the correct classification of their risk according to their number of adenomatous polyps (true positives and true negatives) and will be assigned the correct surveillance interval, whilst other patients will have overestimates of their number of adenomatous polyps (shorter surveillance interval than necessary) and other patients will have underestimates of their number of adenomatous polyps (longer surveillance interval than appropriate). There are also minute risks that diminutive hyperplastic (sessile-serrated) polyps left in the recto-sigmoid area may become cancerous, and that resected and discarded adenomas may be diminutive polyp cancers, which could lead to metastatic cancer. If data allow, these possibilities will be assessed in the model. Depending on risk classification and intervention, patients may be informed immediately of their surveillance interval (low risk, all interventions; other risk levels in resect and discard strategy) or may be informed after histopathology is carried out (for any risk level above low risk where polyps are sent to histopathology).

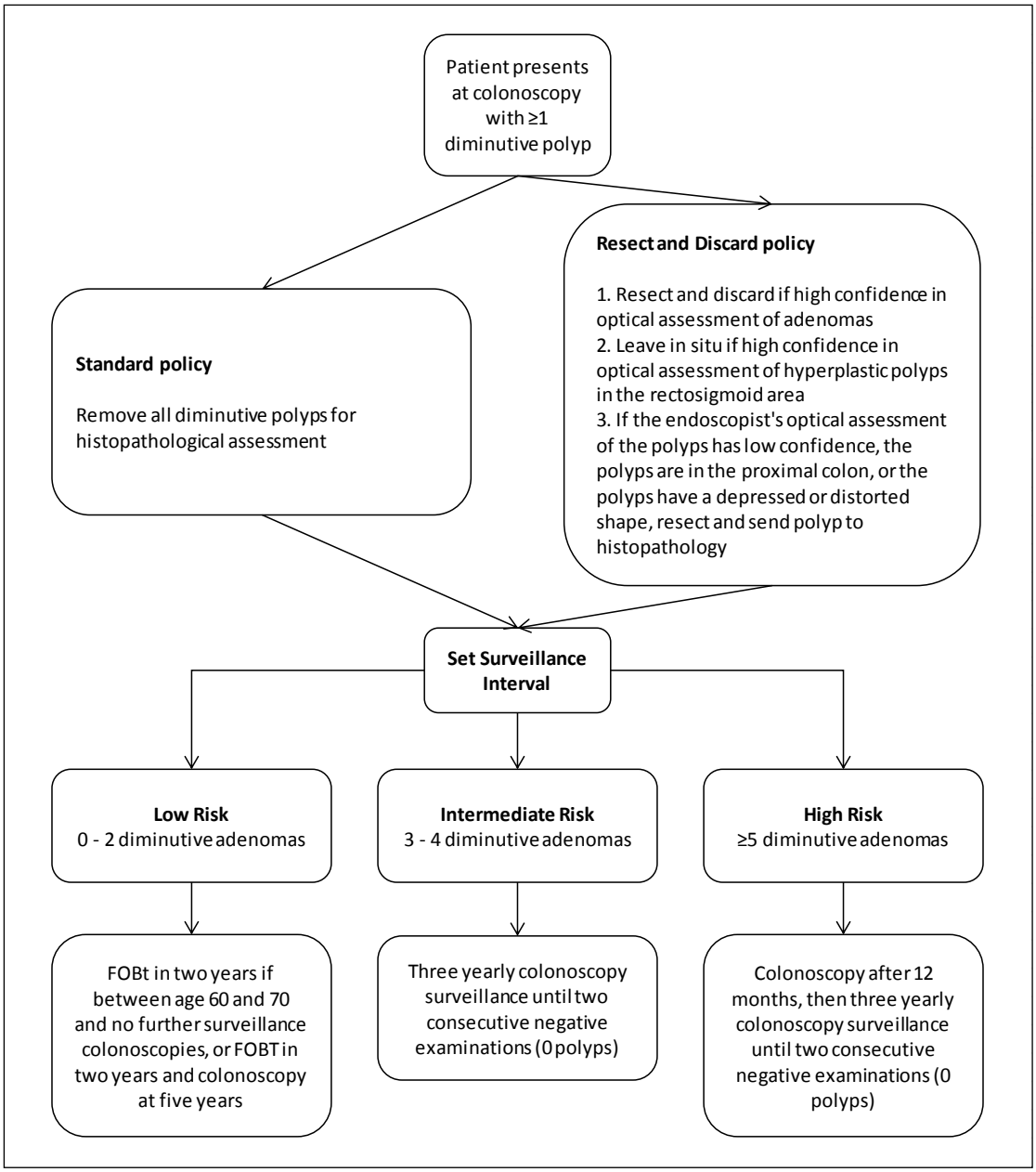


**Figure 1 Patient pathway for surveillance and screening in the economic model**

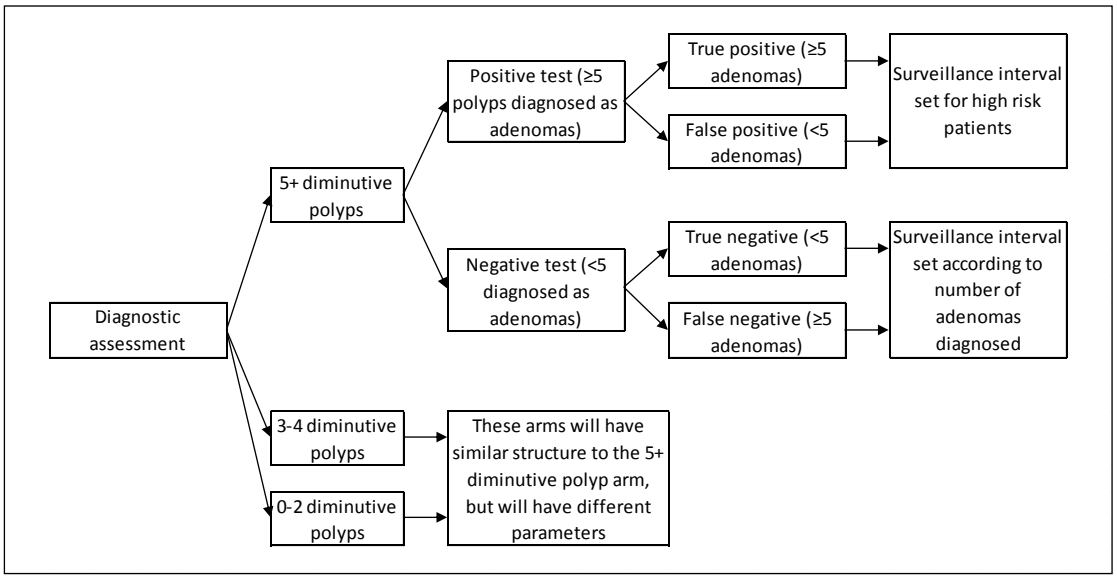


**Figure 2 Demonstrative decision tree structure for diagnostic assessment**

It is anticipated that patients will be further simulated using Markov modelling to capture future health states and long-term outcomes (Figure 3). The model will have a lifetime horizon. Patients will undergo natural disease progression (development of polyps and cancer) as well as screening and surveillance events in the future. The health states will likely be adapted from those described in the Whyte and colleagues' NHS BCSP.[36] The results of our literature searches may alter, replace or refine the presented model structures.

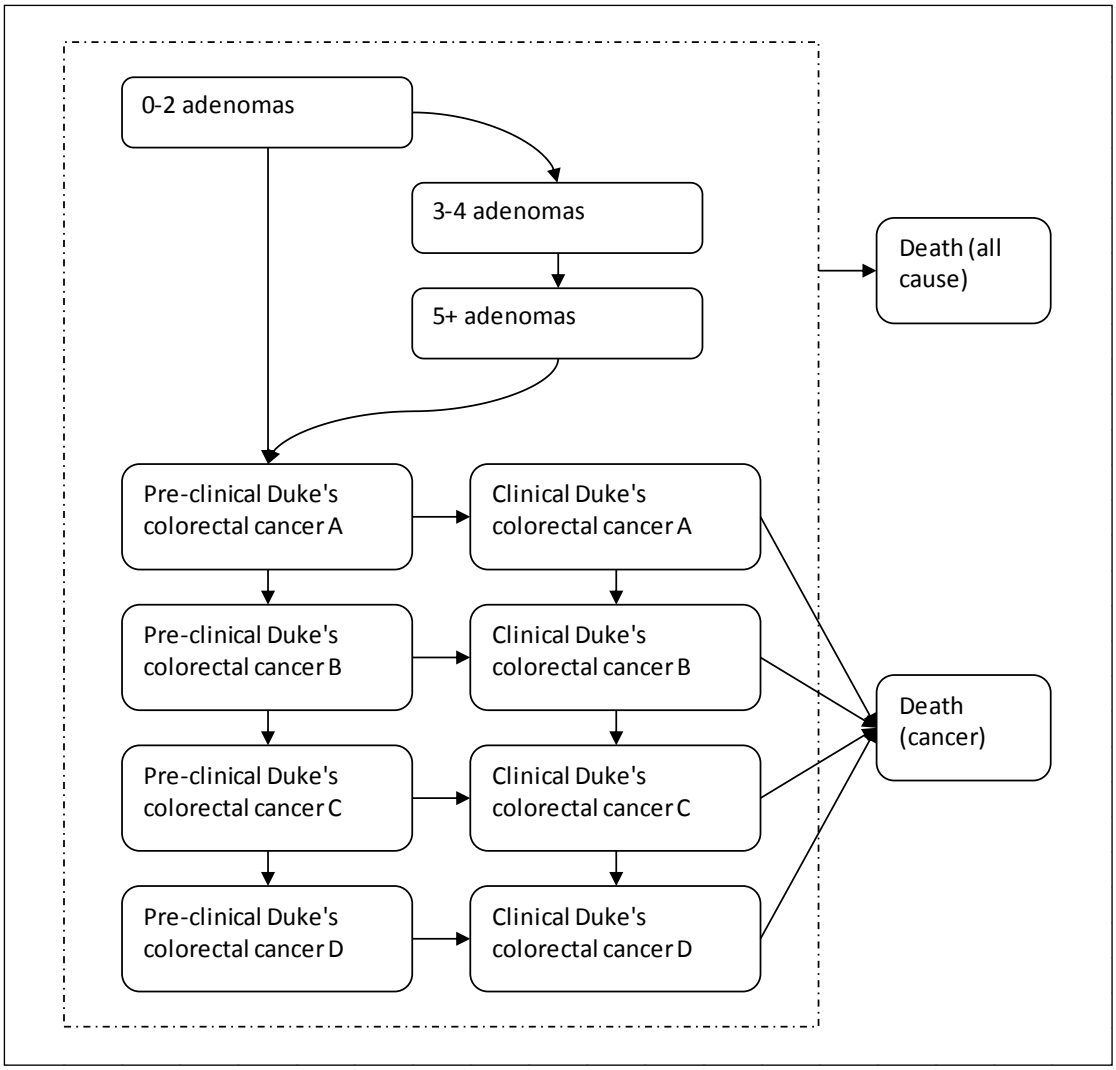


**Figure 3 Preliminary natural history transitions within the model (Whyte and colleagues)[36]**

## 7. Handling information from the companies

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 will be highlighted in yellow and underlined.

## 8. Competing interests of authors

None

## 9. Timetable/milestones

| Milestone | Date to be completed |
|---|---|
| Final protocol | 23/02/16 |
| Progress report to NETSCC, HTA | 25/05/16 |
| Draft report submitted to NICE | 21/07/16 |
| Submission of final report to NETSCC, HTA; NICE | 18/08/16 |

## 10. References


1. NHS Choices. Bowel polyps. Secondary Bowel polyps 13/08/2014 2016. http://www.nhs.uk/Conditions/polyps-bowel/Pages/Introduction.aspx.

2. Kaminski MF, Hassan C, Bisschops R, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2014;**46**(5):435-49.

3. NHS Choices. Endoscopy. Secondary Endoscopy 29/07/2014 2016. http://www.nhs.uk/conditions/endoscopy/pages/introduction.aspx.

4. Varadarajulu S, Banerjee S, Barth BA, et al. GI endoscopes. Gastrointestinal endoscopy 2011;**74**(1):1-6.e6.

5. Manfredi MA, Abu Dayyeh BK, Bhat YM, et al. Electronic chromoendoscopy. Gastrointestinal endoscopy 2015;**81**(2):249-61.

6. Olympus. EVIS LUCERA ELITE Concept Brochure. Japan: Olympus Medical Systems Corp., 2013:8.

7. Olympus. EVIS EXERA III Brochure. USA: Olympus America Inc., 2012:9.

8. Olympus. EVIS LUCERA SPECTRUM family brochure. 2009:7.

9. Fujinon Fujifilm. Fujinon Video endoscopes 500 series scope. Electronic video endoscopy system 4400. Japan: Fujinon Corporation, 2009:13.

10. Pentax Medical. What is i-scan? Secondary What is i-scan? Not provided on webpage 2016. https://i-scanimaging.com/index.php?pg=What is i-scan?&l_id=1.

11. Pentax Medical. i-scan imaging. Secondary i-scan imaging Not provided on webpage 2016. https://www.pentaxmedical.com/pentax/en/95/1/i-scan-imaging/.

12. Kang YK. Diminutive and Small Colorectal Polyps: The Pathologist's Perspective. Clinical endoscopy 2014;**47**(5):404-8.

13. Williams JG, Pullan RD, Hill J, et al. Management of the malignant colorectal polyp: ACPGBI position statement. Colorectal Dis 2013;**15 Suppl 2**:1-38.

14. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointestinal endoscopy 2003;**58**(6 Suppl):S3-43.

15. National Institute for Health and Care Excellence (NICE). Appraisal of docetaxel for early breast cancer through the SingleTechnology Appraisal Process 2005.

16. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012;**143**(3):599-607.e1.

17. Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointestinal endoscopy 1996;**44**(1):8-14.

18. Wada Y, Kudo SE, Kashida H, et al. Diagnosis of colorectal lesions with the magnifying narrow-band imaging system. Gastrointestinal endoscopy 2009;**70**(3):522-31.

19. Wang LM, East JE. Diminutive polyp cancers and the DISCARD strategy: Much ado about nothing or the end of the affair? Gastrointestinal endoscopy 2015;**82**(2):385-8.

20. Rex DK, Kahi C, O'Brien M, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointestinal endoscopy 2011;**73**(3):419-22.

21. Ignjatovic-Wilson A, East JE, Suzuki N, et al. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. Lancet 2009;**10**(12):1171-78.

22. Wanders LK, East JE, Uitentuis SE, et al. Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis. Lancet Oncol 2013;**14**:1337-47.

23. McGill SK, Evangelou E, Ioannidis JPA, et al. Narrow band imaging to differentiate neoplastic and non-neoplastic colorectal polyps in real time: a meta-analysis of diagnostic operating characteristics. Gut 2013;**62**:1704-13.

24. ASGE Technology Committee, Abu Dayyeh BK, Thosani N, et al. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointestinal endoscopy 2015:1-15.

25. Wu L, Li Y, Li Z, et al. Diagnostic accuracy of narrow-band imaging for the differentiation of neoplastic from non-neoplastic colorectal polyps: a meta-analysis. Colorectal Disease 2012;**15**:3-11.

26. Reitsma J, Rutjes A, Whiting P, et al. Assessing methodological quality. In: Deeks J, Bossuyt P, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy 2009.

27. Whiting P, Rutjes A, Reitsma J, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;**3**(25).

28. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. York Publishing Services Ltd.: CRD, 2009.

29. Bossuyt P, Davenport C, Deeks J, et al. Chapter 11. Interpreting results and drawing conclusions. In: Deeks J, Bossuyt P, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version, 2010.

30. Macaskill P, Gatsonis C, Deeks J, et al. Chapter 10. Analysing and presenting results. In: Deeks J, Bossuyt P, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy 2010.

31. National Institute for Health and Care Excellence. Diagnostics Assessment Programme manual. Manchester, 2011.

32. Drummond MF, O'Brien B, Stoddart GL, et al. Methods for the economic evaluation of health care programmes (3rd edition). Oxford University Press 2005.

33. Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 2004;**8**(36):1-158.

34. Hassan C, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2010;**8**(10):865-9, 69.e1-3.

35. Optical diagnosis of small colorectal polyps with resect and discard strategy is cost saving. Gastrointestinal Endoscopy Conference; 2013; Orlando, USA.

36. Whyte S, Chilcott J, Halloran S. Reappraisal of the options for colorectal cancer screening in England. Colorectal Dis 2012;**14**(9):e547-61.

37. Murphy J, Gray A. The cost-effectiveness of immunochemical faecal occult blood testing vs. guaiac faecal occult blood testing for colorectal cancer screening in the NHS Bowel Cancer Screening Programme: Health Economics Research Centre, University of Oxford, 2015.

38. Whyte S, Harnan S. Effectiveness and cost-effectiveness of an awareness campaign for colorectal cancer: a mathematical modeling study. Cancer Causes Control 2014;**25**(6):647-58.

39. Department of Health. Public health functions to be exercised by NHS England: Service specification No.26, Bowel Cancer Screening Programme: Department of Health, 2013.

40. Department of Health. NHS public health functions agreement 2015-16: Public health functions to be exercised by NHS England: Department of Health, 2014.

41. National Institute for Health and Care Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer (CG131): National Institute for Health and Care Excellence (NICE), 2011.

42. Hassan C, Quintero E, Dumonceau JM, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;**45**(10):842-51.

43. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;**59**(5):666-89.

## 11. Appendices

### Appendix 1: Draft Medline search strategy for systematic review of diagnostic studies

1 (virtual and (chromoendoscop* or "chromo endoscop*")).tw. (84)
2 ("real time" and (chromoendoscop* or "chromo endoscop*" or endoscop*)).tw. (1379)
3 (video and (chromoendoscop* or "chromo endoscop*")).tw. (38)
4 (optical and (chromoendoscop* or "chromo endoscop*")).tw. (69)
5 (digital and (chromoendoscop* or "chromo endoscop*")).tw. (21)
6 (magnif* and (chromoendoscop* or "chromo endoscop*")).tw. (252)
7 ("post processing" and (chromoendoscop* or "chromo endoscop*")).tw. (2)
8 ("high contrast" and (chromoendoscop* or "chromo endoscop*" or endoscop*)).tw. (26)
9 ("high definition" and (chromoendoscop* or chromo endoscop*)).tw. (41)
10 ("high resolution" and (chromoendoscop* or "chromo endoscop*")).tw. (77)
11 (electronic and (chromoendoscop* or "chromo endoscop*")).tw. (23)
12 "real time imag*".tw. (2385)
13 "real time histology".tw. (13)
14 ("real- time" and (chromoendoscop* or "chromo endoscop*" or endoscop*)).tw. (1379)
15 "narrow band".tw. (3385)
16 NBI.tw. (813)
17 "narrow* spectrum endoscop*".tw. (1)
18 "optical diagnosis".tw. (104)
19 "optical imaging".tw. (4297)
20 "image enhancement".tw. (662)
21 "EVIS LUCERA ELITE ".mp. (0)
22 "CV-290/CLV-290SL".mp. (0)
23 "CV-260SL/CLV-260SL".mp. (0)
24 "EVIS LUCERA SPECTRUM".mp. (4)
25 "dual focus".tw. (98)
26 ("290HQ" and endoscop*).mp. (0)
27 ("290HQ" and Oympus).mp. (0)
28 ("260HQ" and endoscop*).mp. (0)
29 ("260HQ" and Olympus).mp. (0)
30 FICE.tw. (80)
31 "flexible spectral imaging colour enhancement".tw. (1)

32 (filter* and "white light").tw. (167)
33 "Fuji* intelligent colo?r enhancement".mp. (25)
34 (Fuji* adj5 chromoendoscop*).mp. (20)
35 (Fuji* adj5 endoscop*).mp. (40)
36 "Fujinon/Aquilant Endoscop*".mp. (0)
37 Fuji* Aquilant Endoscop*.mp. (0)
38 "i-scan".mp. (128)
39 "image enhanced endoscop*".tw. (48)
40 "image enhanced chromoendoscop*".tw. (0)
41 "image enhanced chromo endoscop*".tw. (0)
42 (Pentax and endoscop*).mp. (108)
43 (Pentax and chromoendoscop*).mp. (4)
44 "EPK i5000".mp. (0)
45 "EPK i7000".mp. (0)
46 ("high definition" and "video processing").tw. (3)
47 or/1-46 (12991)
48 Colonoscopy/ (20134)
49 colonoscop*.tw. (19205)
50 Colonic Polyps/ (6761)
51 (colon* adj5 polyp*).tw. (7200)
52 (colorectal adj5 polyp*).tw. (4251)
53 Intestinal Polyps/ or Intestinal Polyposis/ or Adenomatous Polyps/ (8159)
54 (intestin* adj5 polyp*).tw. (6944)
55 (adenom* adj5 polyp*).tw. (10257)
56 (diminutive adj5 polyp*).tw. (167)
57 (hyperplas* adj5 polyp*).tw. (2609)
58 Colorectal Neoplasms/ (62453)
59 "colorectal cancer".tw. (58237)
60 (colorectal adj2 neoplas*).tw. (2893)
61 "colon* cancer".tw. (32218)
62 (colon adj5 neoplas*).tw. (1302)
63 or/48-62 (141679)
64 47 and 63 (678)
65 ((chromoendoscop* or "chromo endoscop*") and polyp*).ti. (23)
66 polyp*.tw. (209936)

67 nasal polyp*.tw. (4541)

68 Nasal Polyps/ (5333)

69 67 or 68 (6454)

70 66 not 69 (204658)

71 47 and 70 (372)

72 64 or 65 or 71 (752)

73 limit 72 to animals (91)

74 72 not 73 (661)

**Appendix 2: Draft data extraction form for systematic review of diagnostic studies**

| **Reference and design** | **Diagnostic tests** | **Participants** | **Outcome measures** |
|---|---|---|---|
| **Condition being diagnosed / detected:**<br><br>**First author:**<br><br>**Publication year:**<br><br>**Country:**<br><br>**Study design:**<br><br>**Number of centres:**<br><br>**Funding:**<br><br>**Competing interests:** | **Index test:**<br><br>**Reference standard:** | **Number of participants:**<br><br>**Sample attrition/dropout:**<br><br>**Selection of participants:**<br><br>**Inclusion criteria for study entry:**<br><br>**Exclusion criteria for study entry:** | **Primary outcome of study:**<br><br>**Other relevant outcomes:**<br><br>**Recruitment dates:** |
| **Participant characteristics** | | | |
| **Age, years, mean (SD)** | | | |
| **Other key patient characteristics (list)** | | | |
| **Endoscopist experience and training** | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | | |
| **Sample size calculation** | | | |
| **Results** *(repeat for each sub-group reported)* | | | |
| | **Adenomatous polyps on histopathology** | **Hyperplastic polyps on histopathology** | **Total** |

| | | | |
|---|---|---|---|
| **Index test positive** | a | b | a+b |
| **Index test negative** | c | d | c+d |
| **Total** | a+c | b+d | a+b+c+d |
| **Accuracy** | | | |

*Calculate clinical sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) if possible and note whether these agree with any values that may be reported in the paper. Use https://www.medcalc.org/calc/diagnostic_test.php to assist with calculations*

| ***Diagnosis*** | **Value** | **95% CI** |
|---|---|---|
| **Clinical sensitivity a / (a + c)** | | |
| **Clinical specificity d / (b + d)** | | |
| **PPV a / (a + b)** | | |
| **NPV d / (c + d)** | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | |

Comments: *e.g. Calculations agree with values reported in paper. Note if any cases where 0.5 added to values to avoid division by zero when calculating diagnostic odds ratio. Add an asterisk to denote where values have been calculated by the reviewer.*

*Repeat for other tests/thresholds as appropriate or delete if not required*

| | |
|---|---|
| **Interpretability of test** | |
| **Inter-observer agreement** | |
| **Intra-observer agreement** | |
| **Test acceptability (patients / clinicians)** | |
| **Adverse events** | |
| **High confidence optical diagnosis** | |
| **Low confidence optical diagnosis** | |
| **Number of polyps designated to be left in place** | |
| **Number of polyps designated to be resected and discarded** | |
| **Number of polyps designated for resection and histopathological examination** | |
| **Recommended surveillance interval** | |

| | |
|---|---|
| **Length of time to perform the colonoscopy** | |
| **Number of outpatient appointments** | |
| **Health related quality of life** | |
| **Colorectal cancer** | |
| **Mortality** | |

**Critical appraisal criteria** (based on Reitsma et al.[26] adaptation of the QUADAS Tool[27])

| | **Item** | **Description** | **Judgement** |
|---|---|---|---|
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | | |
| 2 | Is the reference standard likely to classify the target condition correctly? | | |
| 3 | Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? | | |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | | |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | | |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | | |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | | |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | | |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | | |
| 10 | Were uninterpretable/ intermediate test results reported? | | |
| 11 | Were withdrawals from the study explained? | | |

yes / no / unclear