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**Virtual chromoendoscopy for the real-time assessment of colorectal polyps in vivo: a systematic review and economic evaluation**

**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors** Dr Joanna Picot, Senior Research Fellow, SHTAC, University of Southampton, Southampton, UK

Mr Micah Rose, Research Fellow (Health economics), SHTAC, University of Southampton, Southampton, UK

Dr Keith Cooper, Senior Research Fellow (Health economics), SHTAC, University of Southampton, Southampton, UK

Dr Karen Pickett, Research Fellow, SHTAC, University of Southampton, Southampton, UK

Professor Joanne Lord, Director and Professorial Fellow in Health Economics, SHTAC, University of Southampton, Southampton, UK

Ms Petra Harris, Research Fellow, SHTAC, University of Southampton, Southampton, UK

Dr Sophie Whyte, Research Fellow, School of Health and Related Research (ScHARR), The University of Sheffield, Sheffield, UK

Professor Dankmar Böhning, Professor in Medical Statistics, Director of Southampton Statistical Sciences Research Institute, Mathematical Sciences, University of Southampton, Southampton, UK

Dr Jonathan Shepherd, Principal Research Fellow, SHTAC, University of Southampton, Southampton, UK

**Correspondence to** Dr Joanna Picot

Senior Research Fellow

Southampton Health Technology Assessments Centre (SHTAC)

University of Southampton

First Floor, Epsilon House

Enterprise Road, Southampton Science Park

Southampton, SO16 7NS, UK.

Tel: +44(0)23 8059 5921  
 Fax:+44(0)23 8059 5639

email: [j.picot@soton.ac.uk](mailto:j.picot@soton.ac.uk)

www.southampton.ac.uk/shtac

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virtual chromoendoscopy; diminutive colorectal polyps; real-time assessment; diagnostic accuracy; cost-effectiveness; economic evaluation; colorectal cancer; NBI; Narrow band imaging; FICE; Flexible Spectral Imaging Colour Enhancement; i-scan

**ABSTRACT**

**Background:** Current clinical practice is to remove a colorectal polyp detected during colonoscopy and determine whether it is an adenoma or hyperplastic by histopathology. Identifying adenomas is important because they may eventually become cancerous if untreated, whereas hyperplastic polyps do not usually develop into cancer, and a surveillance interval is set based on the number and size of adenomas found. Virtual chromoendoscopy (VCE) (an electronic endoscopic imaging technique) could be used by the endoscopist under strictly controlled conditions for real-time optical diagnosis of diminutive (≤ 5 mm) colorectal polyps to replace histopathological diagnosis.

**Objective:** To assess the clinical-effectiveness and cost-effectiveness of the VCE technologies Narrow band imaging (NBI), Flexible Spectral Imaging Colour Enhancement (FICE), and i-scan for the characterisation and management of diminutive (≤5mm) colorectal polyps using high definition systems without magnification.

**Design:** Systematic review and economic analysis

**Participants:** People undergoing colonoscopy for screening or surveillance or to investigate symptoms suggestive of colorectal cancer

**Interventions:** NBI, FICE and i-scan

**Main outcome measures:** diagnostic accuracy; recommended surveillance intervals; health-related quality of life (HRQoL), adverse effects, incidence of colorectal cancer, mortality, cost-effectiveness of VCE compared with histopathology.

**Data sources**: Electronic bibliographic databases including MEDLINE, EMBASE, The Cochrane Library and DARE were searched for English language published studies from inception to June 2016. Bibliographies of related papers, systematic reviews and company information were screened and experts were contacted to identify additional evidence.

**Review methods:** Systematic reviews of test accuracy and economic evaluations were undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Meta-analyses were conducted where possible to inform the independent economic model. A cost-utility decision analytic model was developed to estimate the cost-effectiveness of VCE compared with histopathology. The model used a decision tree for patients undergoing endoscopy, combined with estimates of long-term outcomes (e.g. incidence of colorectal cancer and subsequent morbidity and mortality) derived from the ScHARR Bowel Cancer Screening model. The model took a National Health Service (NHS) perspective, with costs and benefits discounted at 3.5% over a lifetime horizon. There were limitations in the data on the distribution of adenomas across risk categories, and recurrence rates post-polypectomy.**Results**: Thirty test accuracy studies were included: 24 for NBI, five for i-scan and three for FICE (two studies assessed two interventions). Polyp assessments made with high confidence were associated with higher sensitivity and endoscopists experienced in virtual chromoendoscopy achieved better results than those without experience. Two economic evaluations were included. NBI, i-scan and FICE are cost-saving strategies compared to histopathology and the QALYs were similar between histopathology and virtual chromoendoscopy. The correct surveillance interval would be given to 95% of patients with NBI, 94% of patients with FICE and 97% of patients with i-scan.

**Limitations:** Limited evidence was available for i-scan and FICE and there was heterogeneity among the NBI studies. There is a lack of data on longer-term health outcomes of patients undergoing VCE for assessment of diminutive colorectal polyps.

**Conclusions:** VCE technologies, using high definition systems without magnification, could potentially be used for the real-time assessment of diminutive colorectal polyps, if endoscopists have adequate experience and training

**Future work:** Head-to-head RCTs of the three VCE technologies and more research on the diagnostic accuracy of FICE and i-scan. Longitudinal data on colorectal cancer incidence, HRQoL and mortality.

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LIST OF ABBREVIATIONS

|  |  |
| --- | --- |
| ACPGBI | Association of Coloproctology of Great Britain and Ireland |
| ASGE | American Society of Gastrointestinal Endoscopy |
| BSG | British Society of Gastroenterology |
| CD | Correct diagnosis |
| CI | Confidence interval |
| CRC | Colorectal cancer |
| CRD | Centre for Reviews and Dissemination |
| CDSR | Cochrane Database of Systematic Reviews |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| DARE | Database of Abstracts of Reviews of Effectiveness |
| DISCARD | Detect, InSpect, ChAracterise, Resect and Discard |
| EAG | External Assessment Group |
| EED | Economic Evaluation Database |
| ESGE | European Society of Gastrointestinal Endoscopy |
| FAP | Familial adenomatous polyposis |
| FICE | Flexible Spectral Imaging Colour Enhancement |
| FOBT | Faecal occult blood test |
| FN | False negative |
| FP | False positive |
| GP | General Practitioner |
| HCHS | The Hospital and Community Health Services (HCHS) index |
| HD | High definition |
| HNPCC | Hereditary non-polyposis colorectal cancer |
| HPRC | Hyperplastic polyp(s) resected correct surveillance |
| HPRI | Hyperplastic polyp(s) resected incorrect surveillance |
| HR | High risk |
| HRQoL | Health-related quality of life |
| IBD | Inflammatory bowel disease |
| ICER | Incremental cost-effectiveness ratio |
| ICTRP | International Clinical Trials Registry Platform |
| IR | Intermediate risk |
| JAG | Joint Advisory Group |
| LR | Low risk |
| MAC | Missed adenoma(s) correct surveillance |
| MAHPR | Missed adenoma(s) and hyperplastic polyp(s) resected |
| MAI | Missed adenoma(s) incorrect surveillance |
| NBI | Narrow band imaging |
| NHS | National Health Service |
| NHMRC | National Health and Medical Research Council |
| NICE | NBI International Colorectal Endoscopic |
| NIHR | National Institute for Health Research |
| NAC | Novel Classification System |
| NPV | Negative predictive value |
| PEDro | Physiotherapy Evidence Database |
| PIVI | Preservation and Incorporation of Valuable endoscopic  Innovation programme |
| PPV | Positive predictive value |
| PSSRU | Personal Social Services Research Unit |
| QUADAS | Quality Assessment Tool for Diagnostic Accuracy Studies |
| QALY | Quality-adjusted life year |
| RCT | Randomised controlled trial |
| RevMan | Review Manager |
| ScHARR | School of Health and Related Research, The University of Sheffield |
| SD | Standard deviation |
| SBCS | ScHARR Bowel Cancer Screening |
| SROC | Summary Receiver Operating Curve |
| TN | True negative |
| TP | True positive |
| UEG | United European Gastroenterology |
| UK | United Kingdom |
| UKCTG | UK Clinical Trials Gateway |
| US | United States |
| USA | United States of America |
| USMSTF | US Multi-Society Task Force on Colorectal Cancer |
| VC | Virtual chromoendoscopy |
| WASP | Workgroup serrAted polypS and Polyposis classification |
| WHO | World Health Organisation |
| WLE | White light endoscopy |

**Scientific Summary**

**Background**

Colorectal polyps are small growths on the lining of the colon or rectum. They are common, particularly in people over 60 years of age and they do not usually cause symptoms. Histology can distinguish between polyps that are adenomas and those that are hyperplastic. It is important to identify adenomas because these polyps may eventually become cancerous if undiagnosed and untreated whereas hyperplastic polyps usually do not carry a risk of developing into cancer.

Current clinical practice is to detect colorectal polyps during a colonoscopy when the colon and rectum are examined using conventional white light endoscopy. Dyes may also be used (chromoendoscopy) to enhance visualisation of tissues being inspected. Usually, each detected polyp is removed (by polypectomy) and sent for histopathological examination to determine whether it is an adenoma or hyperplastic. The surveillance interval is set based on the number and size of adenomas found.

An addition to conventional white light endoscopy is virtual chromoendoscopy (VCE), an electronic imaging technique that enables the endoscopist to differentiate between adenomatous and hyperplastic colorectal polyps in real-time during colonoscopy (optical assessment). There are three commercial systems of relevance to this diagnostic assessment report: Narrow band imaging (NBI), Flexible Spectral Imaging Colour Enhancement (FICE), and i-scan. There have been proposals suggesting that virtual chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive (≤ 5 mm) colorectal polyps to replace histopathological diagnosis. The features of these propsals are typically that when the endoscopist has high confidence in the diminutive polyp characterisation, adenomas would be removed and discarded (i.e. not sent to histopathology), whereas hyperplastic polyps would be left in situ (because the risk for colorectal cancer is very low). When the endoscopist cannot confidently characterise a polyp, it would be resected and sent for histopathological examination. The potential benefits of virtual chromoendoscopy, include: fewer polyp resections and possible reduction in associated complications (e.g. bleeding and bowel perforation), patients receiving results faster (so less anxiety associated with waiting for results), and a reduction in health care resource use (e.g. fewer histopathological examinations). However, a potential downside of VCE is that it is not as accurate as histopathology, and so some adenomas may be missed and then left in situ, potentially developing into cancer. For VCE to be incorporated into clinical practice for the real-time assessment of polyps, evidence is needed that it provides an appropriate and efficient standard of care compared to existing practice.

**Objectives**

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 for the characterisation and management of diminutive (≤5mm) colorectal polyps.

**Methods**

*Systematic review of clinical-effectiveness*

We undertook a systematic review of studies assessing diagnostic accuracy and other health outcomes when NBI, FICE and i-scan are used to characterise the histology of diminutive colorectal polyps in real-time. A comprehensive search strategy was designed to capture relevant clinical-effectiveness and cost-effectiveness studies. We searched the following databases from inception to June 2016: MEDLINE, PreMedline In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials(CENTRAL)*,* Database of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment database, and the NHS Economic Evaluation Database (EED). We also identified publications through conference proceedings, websites, bibliographies of included studies and relevant systematic reviews, and our advisory group. Studies were eligible for the review if they were randomised controlled trials (RCTs), prospective longitudinal cohort or cross-sectional studies that evaluated NBI, i-scan or FICE (using high definition endoscopy systems, without magnification) for the real-time diagnosis of diminutive colorectal polyps in people undergoing colonoscopy for screening or surveillance or to investigate symptoms suggestive of colorectal cancer. The reference standard was histopathology with at least one of the following outcomes reported: diagnostic accuracy; number of polyps designated to be left in place, resected, discarded, or sent to histopathology; recommended surveillance intervals; examination time; number of medical consultations; health-related quality of life (HRQoL, including anxiety), adverse effects of polypectomy, incidence of colorectal cancer and mortality. We assessed the risks of bias of the included studies using the QUADAS instrument (Quality Assessment Tool for Diagnostic Accuracy Studies) and narratively synthesised included studies. We conducted bivariate meta-analyses, where possible, to provide pooled estimates of diagnostic sensitivity and specificity for each technology. An advisory group of four independent experts was invited to comment on the protocol and draft report.

*Systematic review of economic studies*

A systematic review of cost-effectiveness studies was conducted to identify relevant evidence to inform the economic evaluation. The review used the same set of references identified in our systematic review of diagnostic accuracy with an additional filter using the keyword ‘cost’. Studies were included if they were a full economic evaluation that included long-term outcomes such as the incidence of colorectal cancer, life years or Quality Adjusted Life Years (QALYs).

*Economic evaluation*

We developed an independent cost-utility decision analytic model to estimate the cost-effectiveness of virtual chromoendoscopy to optically characterise diminutive polyps compared with histopathology. The model used a decision tree for patients undergoing endoscopy, combined with estimates of long-term outcomes (e.g. incidence of colorectal cancer and subsequent morbidity and mortality) derived from the ScHARR Bowel Cancer Screening model (SBCS). The decision tree follows a cohort of patients who receive endoscopy and who have at least one diminutive polyp identified (and no non-diminutive polyps). For the histopathology strategy, all diminutive polyps identified are resected and sent to histopathology. In the base case analysis for virtual chromoendoscopy, polyps characterised with low confidence are resected and sent to histopathology, polyps characterised with high confidence as a hyperplastic are left in situ whereas those characterised as an adenoma are resected and discarded (i.e. not sent to histopathology). The model uses the diagnostic accuracy estimates for virtual chromoendoscopy from our systematic review of diagnostic accuracy. In the long-term SBCS model, patients progress through the development of adenomas, colorectal cancer and subsequent death. Costs are included in the model for colonoscopy, histopathology, adverse events from colonoscopy (polypectomy) and the costs of treating colorectal cancer. Health outcomes are quantified in terms of incremental QALYs, including mortality and impacts on HRQoL associated with adverse effects of polypectomy and colorectal cancer. Costs and benefits are discounted at 3.5% per annum. The perspective of the analysis is that of the NHS and Personal Social Services. The model uses a lifetime horizon and reports results as costs per QALY gained.

**Results**

*Clinical-effectiveness*

From 2070 titles and abstracts screened, 125 full texts were retrieved for detailed examination. The 32 references which met the inclusion criteria described 30 separate studies. Most studies evaluated NBI (n=22) with an additional two studies also evaluating one of the other interventions of relevance (NBI and i-scan, NBI and FICE). Four further studies evaluated i-scan and two further studies evaluated FICE. We assessed the studies to be generally at a low risk of bias across the domains measured by the QUADAS.

The ability of NBI to correctly identify diminutive polyps as adenomas (i.e. the sensitivity of the test) in the whole colon ranged from 55% to 97% (17 studies) for all assessments regardless of endoscopist confidence (studies did not state how high confidence was defined or measured). For high confidence characterisations, sensitivity ranged from 59% to 98% (13 studies) for the whole colon, and from 83% to 96% (five studies) for high confidence characterisations in the rectosigmoid colon. The ability of NBI to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) was typically lower, ranging from 62% to 95% (16 studies) for all assessments in the whole colon, from 44% to 92% (11 studies) for high confidence characterisations in the whole colon and from 88% to 99% (five studies) for high confidence characterisations in the rectosigmoid colon. A bivariate meta-analysis using available data (16 of the 24 NBI studies), produced a summary value for sensitivity of 0.88 (95% CI 0.83 to 0.92) (i.e. 88%) and for specificity of 0.81 (95% CI 0.75 to 0.85) for all characterisations in the whole colon. Bivariate meta-analysis of high confidence NBI characterisations in the whole colon produced summary values for sensitivity of 0.91 (95% CI 0.85 to 0.95) and for specificity of 0.82 (95% CI 0.76 to 0.87) (11 studies), and for high confidence characterisations in the rectosigmoid colon summary values for sensitivity of 0.87 (95% CI 0.80, 0.92) and for specificity of 0.95 (95% CI 0.87, 0.98) (four studies). We found that endoscopists with prior experience of using NBI to characterise diminutive colorectal polyps achieved higher sensitivity and specificity than endoscopists with no prior experience of using NBI.

The five included studies evaluating i-scan varied in how they reported results. One reported results for all polyp assessments in the whole colon, and four reported assessments made in particular parts of the colon. Sensitivity was above 90% in four studies (range: 93% to 95%) and was 82% in a study that used a per patient (rather than per polyp) analysis. Specificity ranged from 83% to 96%. Sensitivity and specificity for high confidence assessments ranged from 94% to 98% and 90% to 96%, respectively. A bivariate meta-analysis of two studies reporting on high confidence characterisations of polyps in the whole colon produced a summary sensitivity of 0.96 (95% CI 0.92 to 0.98) and specificity of 0.91 (95% CI 0.84 to 0.95).

The three included studies evaluating FICE assessed polyps in any part of the colon and did not provide analyses by confidence level. Sensitivity and specificity ranged from 74% to 88% and 82% to 88%, respectively. A bivariate meta-analysis produced a summary value for sensitivity of 0.81 (95% CI 0.73 to 0.88) and for specificity of 0.85 (95% CI 0.79 to 0.90) (three studies).

The negative predictive value (NPV; that is, the probability that patients who are diagnosed by virtual chromoendoscopy as having a hyperplastic polyp truly do not have an adenoma) was more variable across the NBI studies than the FICE or i-scan studies. i-scan had the most consistently favourable results on this outcome, but this may have been due to a higher proportion of the i-scan studies involving endoscopists with prior experience of i-scan.

The percentage agreement between surveillance intervals allocated following NBI (13 studies) and those allocated following histopathology ranged from 84% to 99%. The agreement following i-scan (two studies) ranged from 93% to 97% and for FICE (two studies) from 97% to 100%. When only considering studies in which surveillance intervals were assigned in accordance with the two Preservation and Incorporation of Valuable endoscopic Innovation programme (PIVI) criteria (guidance on the requirements that new technologies should meet before a ‘resect and discard’ strategy can be applied in practice), eight of the nine NBI studies reporting this outcome achieved a level of agreement that was ≥ 90%, thus meeting the first PIVI criterion. Both the i-scan studies reporting this outcome achieved an agreement ≥ 90%. All NBI (five) and i-scan (one) studies that assessed NPV for high confidence assessments of diminutive polyps in the rectosigmoid met the second PIVI criterion of achieving an NPV ≥ 90%. There was no evidence for FICE in relation to the PIVI criteria.

None of the identified studies measured health-related quality of life (HRQoL), anxiety, number of outpatient appointments or telephone consultations, incidence of colorectal cancer or mortality. Four studies assessed adverse effects, stating there were none. Data were too limited on the number of polyps that would be left in place, resected, discarded or sent histopathology, and the time to perform the colonoscopy, for the review to draw conclusions about these outcomes.

*Cost-effectiveness*

We included two studies of virtual chromoendoscopy compared to histopathology in our systematic review of economic evaluations. Both compared a resect and discard strategy with current practice of submitting all polyps to histopathology. The evaluations were published in the USA and found that there were cost savings for the resect and discard group ranging between US$25 and US$174 per person.

In addition, a study by Olympus, the manufacturer of NBI systems, describes a budget impact analysis of NBI for the NHS in England. The decision tree model has a time horizon of seven years and in each year there is a cohort of patients that undergo endoscopy. The study estimated that NBI offers cost savings of £141 million over seven years.

Results of our independent economic model suggest that virtual chromoendoscopy is cost saving compared to histopathology with a mean saving of between £73 and £87 per person over their lifetime for the different VCE technologies. QALYs are similar between histopathology and virtual chromoendoscopy technologies with a very small increase in QALYs for NBI and i-scan compared to histopathology of between 0.0005 – 0.0007 QALYs per person, while FICE is associated with 0.0001 QALYs fewer per person than histopathology. Virtual chromoendoscopy technologies have a cost saving of about £50 per polyp resection avoided compared to histopathology.The model estimates that the correct surveillance interval would be given to 95% of patients with NBI, 94% of patients with FICE and 97% of patients with i-scan. Results are most sensitive to the pathology cost, the probability of perforation with polypectomy and the proportion of patients who die from perforation. Probabilistic sensitivity analyses were conducted for pairwise and incremental comparisons for histopathology with virtual chromoendoscopy technologies. The probabilistic ICERs were similar to the base case deterministic ICERs. At a willingness-to-pay threshold of £20,000 and £30,000, i-scan was most cost effective in 95% and 33% of simulations respectively.

**Discussion**

Evidence was limited for FICE and i-scan, and was generally limited for high confidence characterisations in the rectosigmoid colon. The heterogeneity among the NBI studies in setting, country, endoscopists’ experience and training makes it difficult to determine the diagnostic accuracy of NBI. Uncertainties include the generalisability of the evidence base to the UK, how the settings of studies’ may have impacted on the results (e.g. academic centres compared to community hospitals), and a lack of data on longer-term health outcomes among patients undergoing virtual chromoendoscopy for assessment of diminutive polyps. Studies providing evidence on the diagnostic accuracy of characterising polyps did not relate this to the prediction of surveillance intervals of patients, in order to predict disease progression in patients. The economic analysis includes only diminutive polyps and does not differentiate between the type of polyp such as depressed polyps or sessile serrated polyps. There were limitations in the data available for the prevalence of adenomas across risk classification, the distribution of polyps and the proportion of patients in the higher risk categories with small and large adenomas, which necessitated assumptions in the economics model. There are also limitations in the data on recurrence rates post-polypectomy. The full uncertainty around the model results have not been explored in the PSA as the long-term outcome parameters have not been varied.

**Conclusions**

*Implications for service provision*

Virtual chromoendoscopy technologies, using high definition systems without magnification, have the potential for use in practice for the real-time assessment of diminutive colorectal polyps, if endoscopists have adequate experience and training. NBI and i-scan when used with high confidence generally meet the PIVI requirements to be used to perform a ‘resect and discard’ strategy, but it is unclear how the findings generalise to UK practice. Virtual chromoendoscopy was estimated to be cost saving compared to histopathology. It was associated with a small gain in QALYs for NBI and i-scan and a small decrease in QALYs for FICE. The least costly and most effective of the technologies in terms of diagnostic accuracy was i-scan, which might be explained by the the sparseness of data on diagnostic accuracy for i-scan, and the fact that most of the studies involved experienced endoscopists working in specialist centres.

*Suggested research priorities*

Future research priorities include: head-to-head RCTs of all three virtual chromoendoscopy technologies; more research on the diagnostic accuracy of FICE and i-scan (when used without magnification); further studies evaluating the impact of endoscopist experience and training on outcomes; studies measuring adverse effects, HRQoL and anxiety; and, longitudinal data on colorectal cancer incidence, HRQoL and mortality.

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**Funding details:** The National Institute for Health Research Health Technology Assessment programme project number 15/17/05

Word count: 2,681

**Plain English Summary**

Colorectal polyps are growths in the large bowel. Some polyp types, called adenomas, can develop into bowel cancer if not diagnosed and removed. Specialised doctors or nurses, called ‘endoscopists’ can find polyps when they look at the inner lining of the large bowel (colonoscopy). If a polyp is found, it is removed and sent to a laboratory to see if it is an adenoma (this is called ‘histopathology’). A new technique, called virtual chromoendoscopy, allows the endoscopist to view the polyp in a different way and this can be used during a colonoscopy to help endoscopists decide if a very small polyp (5 mm or smaller) is an adenoma or not, instead of sending the polyp to a laboratory. If the endoscopist is confident the very small polyp is not an adenoma it could be left in the bowel, rather than removed. We aimed to assess the benefits and harms of three virtual chromoendoscopy technologies for diagnosing very small polyps compared to histopathology, and whether these are an effective use of NHS financial resources. We found and reviewed all the studies that had assessed the three technologies [narrow band imaging (NBI), i-scan, flexible spectral imaging colour enhancement (FICE)], using standard methods, and created an economic model. We found the proportion of adenomas that were correctly identified as adenomas by virtual chromoendoscopy, varied between studies from 55% to 97%. Limiting the analysis to the polyp assessments that endoscopists made with high confidence typically increased the proportion of adenomas that were correctly identified as adenomas by virtual chromoendoscopy but results still varied between studies from 59% to 98%. Endoscopists experienced in virtual chromoendoscopy achieved better results than those without experience. Virtual chromoendoscopy techniques were estimated to be cost saving compared to histopathology. The model estimated that NBI and i-scan had slightly better long-term outcomes than histopathology, whilst FICE had slightly worse outcomes. (310 words)

BACKGROUND

* 1. Description of the health problem

Colorectal polyps are small growths (usually less than 1cm in size) on the inner lining of the colon or rectum. They are common, affecting 15-20% of the general population and they usually occur in people who are over 60 years of age.15 Colorectal polyps do not usually cause symptoms though some larger polyps are associated with rectal bleeding, diarrhoea, constipation, and abdominal pain.

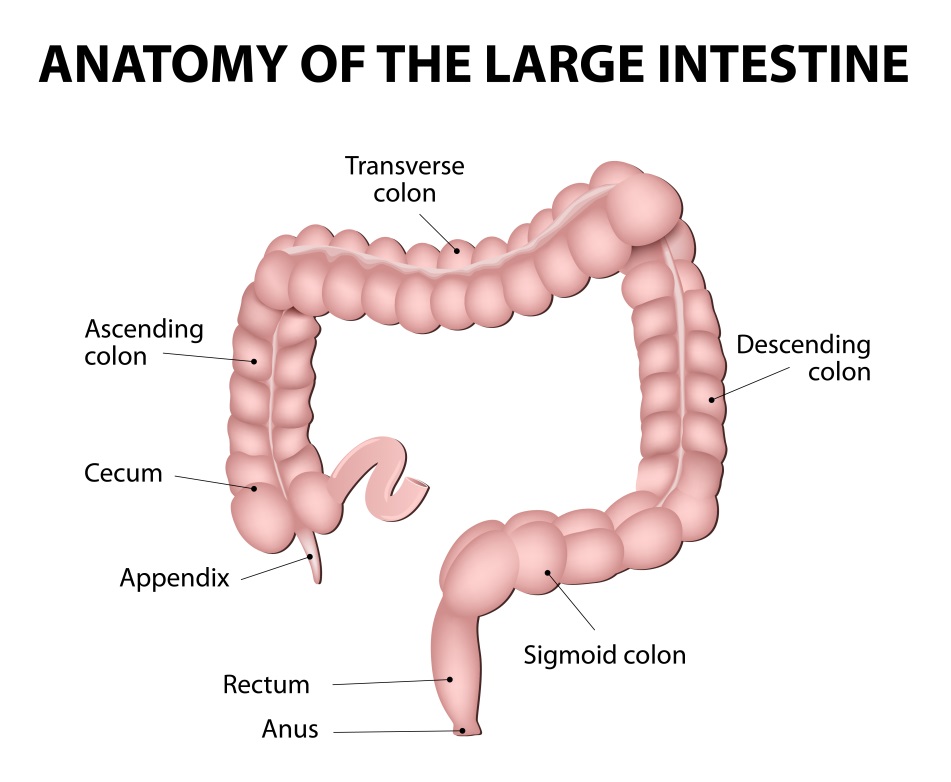
Colorectal polyps can be described in a variety of ways, e.g. by size, according to the type of cell or tissue they arise from within the colon or rectum, according to their shape, and according to their histology.16 Histological classification generally distinguishes between polyps that are adenomatous (known as adenomas, or less commonly, neoplastic polyps), hyperplastic, or deep submucosal invasive cancers. Adenomas may eventually become cancerous if undiagnosed and untreated. Hyperplastic polyps usually do not carry a risk of developing into cancer; however, a subgroup of hyperplastic polyps, called sessile serrated polyps (polyps that have a slightly flattened shape with a saw tooth appearance), also have the potential to develop into cancer.

In terms of size, polyps measuring ≥10mm are referred to as large, whilst those 9mm to 6mm are considered small, and those 5mm or less are classified as diminutive. It has been estimated that 80% of polyps detected at colonoscopy are diminutive.17 A person can have more than one colorectal polyp, and can have polyps of different sizes (e.g. diminutive polyps in addition to small polyps and large polyps). The morphology of a polyp can be described using the Paris endoscopic classification18 (Table 1). For the prediction of malignancy the Association of Coloproctology of Great Britain and Ireland (ACPGBI)19 recommends the use of the Paris endoscopic classification in conjunction with an estimation of the size of a polyp.

Colorectal polyps are usually detected during colonoscopy, a procedure involving examination of the rectum and the colon via a flexible tube called a colonoscope (a type of endoscope). The colonoscope is advanced inside the colon to the cecum (Figure 1) and then slowly withdrawn by the endoscopist who views images of the inner lining on a monitor. Patients might be referred for colonoscopy following an abnormal bowel screening result (see below), or following referral from primary care due to symptoms suggestive of colorectal cancer or of inflammatory bowel disease (IBD), or as part of routine colonic surveillance [e.g. follow-up after previous polyp removal (a polypectomy), or for IBD] (see Section ‎1.3 for details of the care pathway).

Table The Paris endoscopic classification18

|  |  |  |
| --- | --- | --- |
|  | **Type** | **Features** |
| 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 |  |



Designua/Shutterstock.com

Figure Illustration of the large intestine

Colorectal cancer is one of the most common cancers in the UK after breast and lung cancer with approximately 41,900 new cases registered each year.20 The prevalence of colorectal cancer increases with age, with 99% of cases occurring in people aged more than 40 years and 85% in those aged more than 60.21 A family history of bowel cancer is a key risk factor, with the risk increasing according to greater number of first degree relatives affected. 21 Familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) (also known as Lynch syndrome) are inherited genetic disorders that increase the risk of colorectal cancer, though are rare, accounting for only 5% of cancer cases.21 Other factors thought to increase risk of colorectal cancer include diet (e.g. increased consumption of red and processed meat; lack of dietary fibre; lack of fruit and vegetables); obesity and lack of physical activity; consumption of alcohol and use of tobacco; and presence of longstanding IBD (e.g. Crohn’s disease or ulcerative colitis).

The NHS Bowel Cancer Screening Programme offers screening every two years to men and women aged 60 to 74 years. The programme invites eligible adults to carry out a faecal occult blood test (FOBT), which detects small amounts of blood in faeces. People with an abnormal FOBT result are referred for a colonoscopy to determine risk of colorectal cancer.

Upon diagnosis of colorectal cancer patients will undergo staging and grading, with use of biopsy and imaging (e.g. computed tomography, endorectal ultrasonography or magnetic resonance imaging). The Dukes’ classification is a four stage system (A-D) commonly used to determine the size and spread of the cancer. At Dukes’ A the cancer is only in the innermost lining of the bowel or slightly growing into the muscle layer, whilst at Dukes’ D the cancer has spread to other parts of the body such as the liver or the lungs. Treatment of the cancer will depend upon the stage, but commonly includes surgical resection, combined with chemotherapy and radiotherapy where necessary, and in some cases biological therapies.22 Bowel cancer survival rates in England vary according to stage, with rates for Stage 1 patients (known as Dukes’ A colorectal cancer) in the range 95% to 100% at five years or more after diagnosis.20 At Stage 4 (Dukes’ D) survival rates at five years or more are just 5% to 10% (though this could be as high as 40% if liver metastases can be successfully removed by surgery).20 Generally for people with colorectal cancer in England and Wales almost 60% survive their cancer for 10 years or more following diagnosis (based on all stages).20

Description of the diagnostic technologies under assessment

Current clinical practice is to detect colorectal polyps using conventional white light endoscopy. This may be used in combination with dyes (chromoendoscopy) to enhance visualisation of tissues in the area being inspected. Detected polyps are then removed and each is sent for laboratory histopathological examination to determine whether it is an adenoma (therefore at a high cancer risk) or hyperplastic (at a low cancer risk).15 (NB. In some centres some polyps may be left in situ if endoscopists are confident on the basis of white light endoscopy that they are hyperplastic). The aim is to communicate the results to patients within a two week period. Histopathological examination is regarded as the reference standard method for characterising polyps, though it can be associated with errors of measurement and interpretation. For example, concerns have been raised about poor inter-rater reliability between gastrointestinal histopathologists.23 Further, some diminutive polyps may be damaged during resection (or cannot be resected at all), impairing the effectiveness of histopathological analysis.17

Virtual chromoendoscopy refers to electronic endoscopic imaging technologies that provide detailed contrast enhancement of the mucosal surface and blood vessels in the colon and rectum. A number of virtual chromoendoscopy technologies are available. All of these technologies use an endoscopy system typically consisting of an endoscope, a light source, a video processor and a visual display monitor.24,25 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.25

The aim of virtual chromoendoscopy technologies is to provide enhanced visualisation of tissues without the need for dyes, enabling the endoscopist to differentiate between adenomatous and hyperplastic colorectal polyps in real-time during colonoscopy. Virtual chromoendoscopy technologies can be classed as optical or digital. In optical virtual chromoendoscopy, optical lenses are integrated into the endoscope’s light source, which selectively filters white light, resulting in narrow band light. In digital chromoendoscopy, digital post-processing by the video processor is used to enhance the real-time image.26

As discussed in Section ‎2, there are three commercial systems of relevance to this diagnostic assessment report:

* 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 (NBI) (Olympus Medical Systems) is an optical image enhancement technology used in the Olympus endoscopic video imaging systems EVIS LUCERA ELITE,27 EVIS EXERA III28 (not available in the UK) and EVIS LUCERA SPECTRUM.29 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.26,29 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 endoscopist can switch viewing mode from standard white light to NBI and vice versa at any time. 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 in image quality 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 EVIS EXERA system is considered to be comparable with the EVIS LUCERA system in terms of diagnostic performance. The Olympus endoscopy system (including processor, endoscope and annual maintenance) is estimated to cost £87,385.

****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-4400.30 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 based on specific light wavelengths). FICE has ten pre-set wavelength settings which can also be manually altered to achieve the best enhancement of the image.26,30 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. The Aquilant Endoscopy/FujiFilm endoscopy system (including processor, endoscope and annual maintenance) is estimated to cost £59,312.

****i-scan****

i-scan (Pentax Medical) is a digital image processing technology used with Pentax endoscopy systems.31 White light illuminates the area of interest and there are three different algorithms for real-time image processing:26,32

* 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; and (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 equipment enabled with the capability (the EPK-i7000) it is possible to display a normal white light image and an i-scan image simultaneously side by side.32 The Pentax endoscopy system (including processor, endoscope and annual maintenance) is estimated to cost £83,616.

Definition and magnification

The manufacturers of the technologies recommend that high definition endoscopy systems are used to optimise the quality of the image. A high definition system would be one in which the endoscope, the video processor, the display monitor and the cabling are, collectively, capable of producing an image corresponding to 650 to 720 lines of resolution.33 The majority of monitors currently in use would be high definition capable, though not all endoscopes would be high definition. When equipment is due for replacement they will be upgraded to high definition status.

Magnifying endoscopes (also sometimes referred to as near focus or zoom endoscopes) can be used to enhance the clarity of images by magnifying up to 150 times. A movable lens can be fitted to the tip of the endoscope to provide optical zoom. However, magnifying endoscopes are largely unavailable in routine settings as they are not considered practical for day to day use. Most standard endoscopes can provide magnification of up to 35 times at the push of a button.

Classification schemes

Endoscopists make a general assessment of polyps based on observation of elements such as colour, blood vessels and surface pattern. There are several different classification schemes available, with particular schemes used with specific technologies. For example, the NBI International Colorectal Endoscopic scheme was devised specifically for use with NBI.1 The Novel Classification System (NAC) has been developed for use with FICE.34 Examples of classification schemes are shown in Table 2.

Table Examples of virtual chromoendoscopy classification schemes for colorectal polyps

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name of Scheme** | **Basis for classification** | **Classification categories** | | | |
| NBI International Colorectal Endoscopic (NICE) classification1 | 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 classification35 | 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 gyrus-like pits | Type IV | |
| Non-structural pits | Type V | |
| Showa classification36 | 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 | |

A classification system for endoscopic differentiation of small and diminutive adenomas, hyperplastic polyps and sessile serrated adenomas and polyps has recently been developed (the Workgroup serrAted polypS and Polyposis (WASP) classification).37

Training in the use of virtual chromoendoscopy

Training in the use of virtual chromoendoscopy is necessary to ensure adequate endoscopist performance in characterising polyps. Training methods vary, and can involve endoscopists making ex vivo predictions based on still images previously taken using virtual chromoendoscopy, as well as in vivo predictions in real time during colonoscopy under supervision of an endoscopist more experienced in use of the technology. The duration of training may vary, with endoscopists subject to post-training key performance indicators and auditing. For example, the manufacturers of NBI estimate that a one to two day initial course would be sufficient. An online computer training App can be used as refresher training, in conjunction with audits and use of a validated classification scheme. Results of a recent study in England showed that a learning curve is observed in practice even for endoscopists experienced in in-vivo colorectal polyp characterisation.38 A 90% threshold for diagnostic accuracy was achieved with use of high definition white light endoscopy followed by i-scan once 200 polyps (<10mm in size) had been examined. This suggests that, following initial training, endoscopists should receive regular feedback on the accuracy of their diagnostic predictions (e.g. via histopathology on small batches of polyps) until an acceptable level of accuracy has been reached. This may take up to six months depending on the volume of colonoscopies performed. Criteria for diagnostic performance of virtual chromoendoscopy have been proposed by international guidelines (see Section ‎1.3), which specify the need for endoscopists to be adequately trained and audited. The Joint Advisory Group (JAG) on gastrointestinal endoscopy has issued key performance indicators and quality assurance standards for colonoscopy39 and offers accreditation for colonoscopists, though there is no accreditation specifically for virtual chromoendoscopy.

Care pathway

Figure 2 provides an illustration of the care pathway showing indications for colonoscopy and subsequent management, reproduced from the National Institute for Health and Care Excellence scope for this diagnostic assessment.40 As mentioned in Section ‎1.1, patients may be referred for colonoscopy via a number of routes. For example, they may receive colonoscopy following an abnormal bowel cancer screening result, or after referral from primary care due to symptoms suggestive of colorectal cancer (e.g. rectal bleeding, pain, or altered bowel habits).



Figure reproduced with permission from the National Institute for Health and Care Excellence Scope for this appraisal40

Figure Care pathway before and after colonoscopy

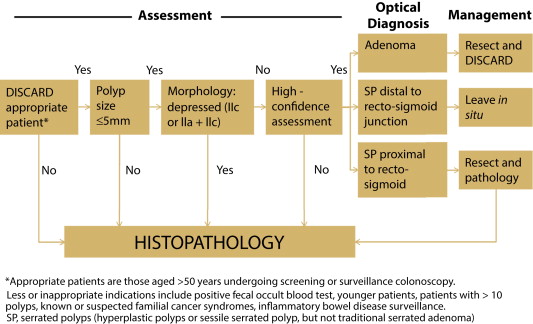
The risk of colorectal cancer varies between different patient groups. Patients with FAP and HNPCC (Lynch syndrome) have a high risk of colorectal cancer. Patients with an abnormal bowel cancer FOBT result may be at higher risk than patients undergoing surveillance for removal of adenomatous polyps.

Following the detection of colorectal adenomas by colonoscopy, a surveillance interval will be set, based on the size and number of adenomas found. The British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland have issued guidelines for colorectal cancer screening and surveillance in moderate and high risk groups.41 The following recommendations are made:

* people with 1 or 2 small (less than 1 cm) adenomas are at low risk, and need no colonoscopic surveillance or 5-yearly surveillance until one negative examination then cease surveillance.
* people with 3 or 4 small adenomas or at least 1 adenoma this is 1 cm or larger are at intermediate risk and should be screened 3-yearly until two consecutive examinations are negative.
* people with 5 or more adenomas, or 3 or more adenomas at least one of which is 1 cm or bigger, are at high risk and an extra examination should be undertaken at 12 months before returning to 3-yearly surveillance.

The National Institute for Health and Care Excellence clinical guideline 118 on colonoscopic surveillance in people with IBD or adenomas makes similar recommendations.42

Virtual chromoendoscopy takes place in secondary or tertiary care at the same point in the care pathway as current clinical practice using conventional white light endoscopy or dye-based chromoendoscopy. It is likely that virtual chromoendoscopy technologies would be used alongside conventional 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. For example, the endoscopist may begin examining the colon with white light endoscopy, and then (in some cases) use dye to enhance visualisation of potential adenomas. They may then switch the endoscope to use virtual chromoendoscopy to further enhance visualisation. This practice is referred to as optical assessment of colorectal polyps. The care pathways would diverge when a diminutive polyp of ≤ 5mm is detected. Under current clinical practice a diminutive polyp identified by conventional white light endoscopy would be removed and sent for histopathological examination to determine whether it is adenomatous, hyperplastic, or cancerous.43 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 rectosigmoid colon would be left in situ (as these would be considered very low risk for colorectal cancer). This is referred to as the DISCARD strategy (Detect, InSpect, ChAracterise, Resect and Discard)17 (Figure 3). 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. The level of confidence with which polyp classifications are made is subjective and varies between endoscopists. Some endoscopists increase objectivity by referring to the relevant classification system, e.g. a high confidence assessment made with NBI might be based on whether at least two of the NICE classification criteria apply to the particular polyp (i.e. based on polyp colour, vessels and surface pattern).



Reprinted from Gastrointestinal Endoscopy, 82/2, Wang L.M. and East J.E. Diminutive polyp cancers and the DISCARD strategy: Much ado about nothing or the end of the affair? Pages 385-8. Copyright (2015), with permission from Elsevier

Figure Flow chart for low-risk application of the DISCARD strategy for diminutive colorectal polyps (from Wang and East, 2015)17

Advantages of the DISCARD strategy include the fact that real-time characterisation of polyps may potentially alleviate patient anxiety associated with waiting for histopathology results and reduce health service and patient costs associated additional appointments. A surveillance interval can be set on the day of the procedure, rather than at a follow-up appointment following the results of histopathology and savings may be made through reduced use of histopathology. It has been reported that histopathology accounts for up to 10% of the cost of colonoscopy,17 and that use of colonoscopy in the NHS is increasing each year.

There may be potential disadvantages associated with the use of virtual chromoendoscopy. For example, endoscopists will need to have sufficient experience with in-vivo characterisation of polyps and adequate training in, and experience of, the particular virtual chromoendoscopy technology. This is a requirement of European and American endoscopy guidance (see Section ‎1.3.1). It has been noted that performance among community-based endoscopists may not necessarily meet these requirements.17 Furthermore, there is the risk that a diminutive polyp cancer (incidence rates of which vary from 0% to 0.6%17) may inadvertently be characterised as an adenoma, resected and discarded without histopathological examination, with malignant cells left behind, and subsequent potential development of undiagnosed metastatic disease and death.17 To attempt to address these concerns, international professional associations have issued guidance on the use of virtual chromoendoscopy as part of a DISCARD strategy, discussed next.

Diagnostic thresholds and requirements for use of virtual chromoendoscopy

There are several different aspects to any decision to implement the new technology and European43 and American guidance44 has been published.

The European guidance,43 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 (≤ 5 mm) colorectal polyps to replace histopathological diagnosis. The optical diagnosis has to be reported using validated scales, must be adequately photo-documented, and can be performed only by experienced endoscopists who are adequately trained and audited (ESGE describe this as a weak recommendation based on high quality evidence).

The American guidance44 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 (ASGE). The PIVI statement defines two requirements, which new technologies for the real-time endoscopic assessment of the histology of diminutive colorectal polyps should meet, before a ‘resect and discard’ strategy could be applied:

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 rectosigmoid 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.

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 permanently stored and should be of sufficient resolution to support the endoscopists' assessment and clinical decisions.

Current service provision

As stated above, current practice is to detect polyps using white light endoscopy, with additional dye based chromoendoscopy used where necessary to provide additional information on polyp characteristics. All diminutive polyps detected are resected and undergo histopathological analysis to determine whether they are adenomatous or hyperplastic. A surveillance interval is then set based on the number and size of adenomas detected. The majority of existing endoscopy systems in use in NHS hospitals are thought to be capable of virtual chromoendoscopy. The technology is built into the light source and video processor and can be activated by the endoscopist by a switch at any time during colonoscopy. The lifecycle of an endoscopy system is estimated to be between five and eight years, and all new systems are now equipped with virtual chromoendoscopy technology. However, virtual chromoendoscopy and the DISCARD strategy is not thought to be routinely used as a management protocol. However in some centres diminutive polyps in the rectosigmoid colon are optically diagnosed using white light or virtual chromoendoscopy and left in place if there is high confidence the polyps are hyperplastic. Of the three technologies of relevance to this assessment, NBI is considered to be the most widely available, and it has the largest market share for electro-medical service contracts in England.

1. DEFINITION OF THE DECISION PROBLEM

Under current clinical practice all diminutive polyps (1-5 mm in size) identified by conventional white light endoscopy would be removed and sent for histopathological examination to determine whether they are adenomas or hyperplastic, and the consequent colorectal cancer risk. Once histopathology results are available a surveillance interval is set according to the number and size of adenomas detected. Use of a virtual chromoendoscopy technology would provide the endoscopist with enhanced visualisation to differentiate between adenomas which could be resected and discarded (i.e. not sent for histopathological assessment) and hyperplastic polyps in the rectosigmoid colon which could be left in situ. This can only be done when the endoscopist is highly confident in their characterisation of the polyp.

The potential benefits of virtual chromoendoscopy 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 results more quickly, thus potentially reducing patient anxiety; a reduction in health resource use through fewer histopathological examinations; and management (including surveillance) decisions could also be provided more quickly. 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.43

In order for virtual chromoendoscopy technologies 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?

Populations and relevant subgroups

The population of relevance to this assessment is: people referred for colonoscopy through the NHS Bowel Cancer Screening Programme because of an abnormal FOBT test result; people offered colonoscopic surveillance because they had adenomas previously removed; and people undergoing colonoscopy with diminutive colorectal polyps referred for colonoscopy by a GP because of symptoms suggestive of colorectal cancer.

At the scoping stage of this assessment it was agreed that patients with IBD, or conditions such as FAP or HNPCC would not be relevant, as these are distinct patient groups with increased risks of colorectal cancer in whom differentiation between adenomatous and non adenomatous polyps during colonoscopy is more complicated (e.g. in patients with IBD because of factors such as increased amount of microvessels). Virtual chromoendoscopy with a DISCARD strategy would be unlikely to be used in these patients.22 At the scoping stage it was also considered that small polyps (6-9mm in size) would not be included in the scope of the assessment.22

Index tests

Virtual chromoendoscopy is the index test, of which three technologies are considered relevant to this diagnostic assessment. These are:

* NBI
* FICE
* i-scan

Each technology should be used with high definition or high resolution monitors and endoscopes without the use of magnification.

Reference standard

The reference standard for virtual chromoendoscopy is histopathological assessment of diminutive polyps.

Outcomes

A range of outcomes are relevant to this assessment, which can be classified as diagnostic test accuracy [e.g. accuracy (i.e. proportion of correctly classifiedpolyps among all the polyps), sensitivity, specificity, accuracy, negative and positive predictive values], intermediate outcomes (e.g. recommended surveillance intervals, time taken to perform colonoscopy), patient reported outcome measures (e.g. health-related quality of life), clinical outcomes (e.g. adverse effects of polypectomy, incidence of colorectal cancer) and cost outcomes (e.g. endoscopy system costs, colonoscopy and related costs, training costs, histopathology costs).

Overall aims and objectives of assessment

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.

1. METHODS

We set out the methods for the systematic reviews of clinical and cost-effectiveness a priori in a research protocol, which was published on the National Institute for Health and Care Excellence’s website (<https://www.nice.org.uk/guidance/GID-DG10004/documents/final-protocol>). The protocol was also registered with PROSPERO, a prospective register of systematic reviews (registration ID: CRD42016037767).45 Our expert advisory group commented on a draft of the protocol. The reviews were undertaken following the general good practice approaches recommended by the Centre of Reviews and Dissemination (CRD),46 the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy,47,48 and the National Institute for Health and Care Excellence Diagnostics Assessment Programme Manual.49 Here, we outline the methods specified in the protocol and note minor modifications that were made during the review.

* 1. Identification of studies

An experienced information specialist developed and tested a comprehensive search strategy. The strategy was designed to identify studies of the diagnostic accuracy of virtual chromoendoscopy and studies providing relevant clinical outcomes (morbidity, mortality, HRQoL) associated with virtual chromoendoscopy and histopathological diagnosis. The strategy was also designed to capture relevant cost-effectiveness studies, to inform the economic evaluation (Section ‎5).

The following databases were searched from inception to June 2016 for published research: MEDLINE, PreMedline In-Process & Other Non-Indexed Citations, EMBASE, Web of Science, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment database, and NHS Economic Evaluation Database (EED). (NB. The protocol for the systematic reviews stated that the Medion database of diagnostic studies would be searched; however, when the review commenced we found that this database had been discontinued.) Grey literature and ongoing studies were also identified, through searches of the following databases in March 2016: UK Clinical Trials Gateway (UKCTG), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ISRCTN (controlled and other trials), clinicaltrials.gov, and PROSPERO. (NB. The protocol for the systematic reviews stated that the UK Clinical Research Network Portfolio Database and the NIHR Clinical Research Network Portfolio would be searched but these are now part of the UKCTG). All searches were limited to the English language.

We additionally searched conference proceedings and the internet pages of relevant organisations for publications, both in April 2016. Proceedings from the following conferences were searched: 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; and, United European Gastroenterology (UEG) Week Conference. We searched the following organisations’ websites: the British Society of Gastroenterology, the European Society of Gastrointestinal Endoscopy, ASGE, and the American Gastrointestinal Association.

We also searched the bibliographies of the included studies and of relevant systematic reviews found during the searches to identify further references, and asked our advisory group of experts to identify additional published and unpublished studies. Information provided by the companies to the National Institute for Health and Care Excellence was also searched for additional studies that might meet the review inclusion criteria. A full list of databases searched, search dates and an example search strategy are provided in Appendix 1.

* 1. Inclusion and exclusion criteria

We screened all the publications identified from the searches against the pre-specified eligibility criteria set out here, to determine if they should be included in the reviews of clinical effectiveness and cost-effectiveness.

**Study design**

For the systematic review of clinical effectiveness, studies were eligible for inclusion if they were Randomised Controlled Trials (RCTs), prospective longitudinal cohort studies or cross-sectional studies. Systematic reviews were not included and were only retrieved during screening to check their reference lists for potentially relevant primary research studies. Editorials and case-reports were not included.

For the systematic review of cost-effectiveness, studies were included if they were full economic evaluations, assessing costs and consequences, of the specified virtual chromoendoscopy technologies.

**Population**

For both the reviews of clinical effectiveness and cost-effectiveness, studies had to include at least one of the following populations to be eligible for inclusion in the review:

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

As stated earlier (Section ‎2.1.1) the target population in this assessment does not include people undergoing monitoring for IBD (e.g. Crohn’s disease); and people with polyposis syndromes such as HNPCC or FAP. Studies including these populations were therefore excluded.

**Index test**

Studies were included in both reviews if they evaluated one or more of the technologies of interest for the real-time diagnosis of colorectal polyps (as opposed to post-procedure image-based diagnosis):

* NBI - EVIS LUCERA ELITE, EVIS LUCERA SPECTRUM or EVIS EXERA (Olympus Medical Systems). The EXERA system is not available in the UK but expert advice to the External Assessment Group (EAG) was that diagnostic outcomes are similar to the EVIS LUCERA series.
* FICE (Fujinon/Aquilant Endoscopy)
* I-scan (Pentax Medical)

Studies of these technologies were only included if they used high definition or high resolution endoscopy systems, without the use of magnification (in at least one study arm, in the case of RCTs; arms not meeting this criterion were excluded). These limitations were applied, because, as explained in section ‎1.2.4, the majority of endoscopy equipment used in practice is (or will be in the future) high definition capable and because magnifying endoscopes are largely unavailable and not considered practical in routine care. During screening, the following decision rules were created to address uncertainty about inclusion of studies in the clinical effectiveness review when they used inbuilt or optional magnification or did not mention magnification:

* studies or study arms using inbuilt (close focus) magnification (which is a low level of magnification, e.g. ×1.5) that did not require a zoom endoscope or any additional equipment were included.
* when magnification was described as optional and no further details were provided or when magnification was not mentioned, we erred on including the study (i.e. presumed no magnification).

Additionally, if a standard definition endoscope was used with a high definition monitor in a study, we excluded the study as this type of monitor cannot compensate for lack of a high definition endoscope. Studies or study arms using endoscopes with a push-button ‘near focus’ capability were excluded, as these endoscopes use magnification, unless it was clear that the ‘near focus’ function had not been used during polyp characterisation.

**Reference test (Comparator)**

Only studies using histopathological assessment of resected diminutive (≤5 mm in size) colorectal polyps as the reference test were included the reviews. Studies of larger sized polyps were eligible if outcome data were given for a sub-group of diminutive polyps.

**Outcomes**

Studies had to measure and report results for at least one of the following outcomes to be included in the clinical effectiveness review (none were specified as primary or secondary outcomes for the review):

* Accuracy of virtual chromoendoscopy diagnosis 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
* Health-related quality of life (HRQoL), including anxiety
* Adverse effects of the removal of polyps (i.e. of polypectomy)
* Incidence of colorectal cancer
* Mortality

To be included in the cost-effectiveness review, studies needed to measure relevant outcomes including life years, incidence of colorectal cancer or Quality Adjusted Life Years (QALYs).

* + 1. Inclusion screening process

Reviewers selected studies for inclusion through a two-stage process using the predefined and explicit criteria specified above. Two reviewers independently assessed the titles and abstracts of the publications identified through the searches for potential relevance to the review. We then obtained the full texts of agreed potentially relevant publications for full text screening. During full text screening, one reviewer assessed each publication against the eligibility criteria, using a standardised inclusion flow chart, and another reviewer checked the first reviewer’s decision and a final decision regarding inclusion was agreed. Studies had to meet all of the eligibility criteria to be included in the review. At both stages any disagreements were resolved by discussion, with involvement of a third reviewer where necessary. The inclusion flow chart is shown in Appendix 2. The first item in the flowchart that the reviewers agreed would be a reason for exclusion was recorded as the primary reason for exclusion.

During full text screening, we found that the population was unclear in some of the publications assessed (e.g. due to lack of description). In these instances, we erred on including the study in the review, unless there was evidence that it included a population not relevant to this assessment (e.g. inflammatory bowel disease, polyposis syndromes). Studies published as abstracts or conference proceedings were only included in the reviews if they were published in 2014, 2015 or 2016 and if sufficient details were presented to allow appraisal of the methodology and assessment of results to be undertaken (as pre-specified in the protocol).

* 1. ****Data extraction strategy****

One reviewer extracted data from each included study, using a standardised and pilot-tested data extraction form, and a second reviewer checked the extracted data for accuracy. Reviewers resolved any discrepancies in the data extracted through discussion or, where necessary, arbitration by a third reviewer. Publications that reported the same primary study were data extracted together as one study, to avoid double-counting information. Reviewers extracted data, where available, on the study and population characteristics, the endoscopic equipment used (including model numbers), the study endoscopists’ experience and training, the polyp classification system used, the sample size calculation, and results for all outcomes of interest in this review. Where data were available, we extracted the results of subgroup analyses of diagnostic accuracy by the endoscopists’ level of expertise and experience in optical assessment of polyps, their level of confidence in their polyp assessment (i.e. high or low), and the location of the polyp. See Appendix 3 for the completed data extraction form for each study.

When we extracted the diagnostic accuracy results from each study, we used available data in the study publication(s) to populate a 2×2 contingency table showing how the index test results related to the histopathological analysis results, for each analysis or subgroup analysis of diminutive polyps. The contingency tables showed the number of true positives, false positives, true negatives and false negatives. Where these data were only partially reported in the study publications or not reported at all, reviewers imputed the data from other available results information, if possible. It was necessary to extract or impute these data, as we needed complete 2×2 tables to be able to include a study in a meta-analysis (see Section 3.5 for further details about data synthesis). It was not always possible to impute these data (e.g. total number of diminutive polyps not reported and numbers of adenomas and hyperplastic polyps not reported). We contacted the contact study author for five studies to request the 2x2 table data. Two authors replied but neither were able to supply data. Reviewers also calculated the accuracy (proportion of correctly classified polyps among all the polyps), clinical sensitivity, clinical specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio for each diagnostic accuracy analysis and subgroup analysis reported in each study. Reviewers compared the values they calculated with the study values and noted any discrepancies. If any of these outcomes had not been reported in the studies, the reviewer’s calculated values were used. We used an online calculator MedCalc (https://www.medcalc.org/calc/diagnostic\_test.php) to calculate clinical sensitivity, clinical specificity, PPV, NPV, and positive and negative likelihood ratios.

* 1. Quality assessment

The quality of studies reporting diagnostic accuracy was assessed using the Cochrane Collaboration adaptation50 of the QUADAS tool (Quality Assessment Tool for Diagnostic Accuracy Studies)51 which can be used to assess a variety of study designs (e.g. RCT, non-RCT, prospective cohort studies). Table 3 shows the types of bias assessed by the QUADAS tool and how these we assessed whether these types of bias were present in studies in this review. One reviewer assessed the methodological quality of each study and a second reviewer checked the first reviewer’s judgements, with any disagreements resolved by consensus or if necessary by arbitration by a third reviewer.

Table Types of bias assessed by the QUADAS tool and their application to studies of the accuracy of virtual chromoendoscopy for the real-time assessment of colorectal polyps in vivo

|  |  |  |
| --- | --- | --- |
| **QUADAS question** | **Type of bias** | **Explanation** |
| 1 | Spectrum bias | The study population is not representative of those who will receive the index test (virtual chromoendoscopy i.e. NBI, i-scan or FICE) in clinical practice |
| 2 | Verification bias | The reference standard (histopathology) does not accurately distinguish between adenomas and hyperplastic polyps |
| 3 | Disease progression bias | The time interval between the index (virtual chromoendoscopy) test and reference standard (histopathology) is long enough that the two tests may not have measured the same disease state |
| 4, 5a | Differential verification bias | Diagnosis is inaccurate because not all patients receive the same reference standard |
| 6 | Incorporation bias | The index (virtual chromoendoscopy) test is not independent of the reference standard (e.g. if it was one of several tests used as the reference standard) |
| 7 | Diagnostic review bias | The index test (virtual chromoendoscopy) result influences interpretation of the reference standard result |
| 8 | Test review bias | The reference standard result influences interpretation of the index (virtual chromoendoscopy) test result |
| 9 | Clinical review bias | The information used when interpreting the index (virtual chromoendoscopy) test does not reflect that likely to be available in clinical practice |
| 10 | Test classification bias | If index test results classified as uninterpretable, intermediate or indeterminate are incorrectly included or excluded from the analysis, this may systematically influence sensitivity or specificity |
| 11 | Attrition bias | The exclusion of patients or test results from the analysis may systematically influence sensitivity or specificity if   * the reason for exclusion is linked to test performance * if criteria for permitting exclusions differ between tests   This is particularly the case if the magnitude of attrition is unbalanced across the test methods |

a Two QUADAS questions assess differential verification bias.

* 1. Method of data synthesis

The included studies were synthesised in a narrative review with tabulation of results. Meta-analysis was also conducted to provide pooled estimates of diagnostic sensitivity and specificity. The rationale for meta-analysis was to provide a more precise estimate of diagnostic accuracy than can be provided from single studies alone. In diagnostic test studies, sensitivity and specificity are often negatively correlated, sometimes because studies have used different thresholds for defining positive and negative test results. Furthermore, heterogeneity often exists between the studies, in terms of patient characteristics, settings, and tests used. These factors need to be taken into account in the choice of meta-analysis methods applicable to a given topic. A univariate meta-analysis pools sensitivity and specificity separately, failing to take into account the correlation. Hierarchical models include statistical distributions at the lower level (within-study variability in sensitivity and specificity) and at the higher level (between-study variability) and can therefore take into account correlation and heterogeneity.52 In this systematic review it is likely that heterogeneity exists in factors such as the endoscopist’s level of experience and training in virtual chromoendoscopy, the setting in which colonoscopy is performed, and the patient’s indication for colonoscopy and therefore their risk of colorectal cancer. Virtual chromoendoscopy does not require an explicit numerical threshold for a diagnostic prediction. Rather, the prediction is a binary one, of whether a polyp is an adenoma or hyperplastic. A hierarchical bivariate meta-analysis model was used in this assessment as it estimates summary sensitivity and specificity at a various thresholds (in this case the threshold is the confidence and judgement with which the endoscopist makes their polyp characterisation).53 Previous published meta-analyses of virtual chromoendoscopy for optical diagnosis of colorectal polyps have also used a bivariate model to estimate pooled sensitivity and specificity.54-56

We conducted separate meta-analyses for the each of the three respective virtual chromoendoscopy technologies relevant to this report compared with histopathology. For each technology we produced individual meta-analyses according to the level of confidence with which the polyp characterisation had been made by the endoscopist in accordance with how the data were reported in the primary studies (high confidence predictions; all predictions irrespective of confidence level). High confidence predictions are of particular relevance to the DISCARD strategy and are used to inform the economic model in this assessment report (see Section ‎5.2). We also meta-analysed studies according to the area of the colon in which the polyps were located and thus characterised (e.g. whole colon, rectosigmoid colon), stratified according to level of endoscopist confidence in making characterisations. Again, this is relevant to the DISCARD strategy for decisions about whether hyperplastic polyps in the rectosigmoid colon can be left in situ (see Section ‎1.3). Where possible we explored heterogeneity by conducting sub-group analyses for factors such as the level of experience of the endoscopist in the in vivo characterisation of polyps, and in using the specific virtual chromoendoscopy (see Section ‎4.1.1 for a description of the studies included in the systematic review).

Consideration was given to meta-analysing NPVs from the included studies. An NPV of ≥90% is required for a high confidence decision to leave a suspected hyperplastic diminutive polyp in place, as stated in the PIVI initiative44 (see Section ‎1.3). However, PPVs and NPVs vary with differences in disease prevalence, so pooling is not always advisable when it is suspected that there may be variation in prevalence between studies.49 Because the prevalence of adenomas and hyperplastic polyps may vary between studies [e.g. due to differences in case mix (screening, surveillance and symptomatic populations) and patient characteristics (age, sex)] we chose not to pool NPV values across studies.

We used Stata software (Stata 14.0 IC, Stata Corp, Texas) to conduct the meta-analysis, using the metandi Stata package which has been specifically designed to perform bivariate meta-analyses of diagnostic studies.57 The Stata package xtmelogit was also used where fewer than four studies were available in a meta-analysis, as metandi was not able to perform analyses on this number of studies. We used Stata programming code supplied by the Cochrane Screening and Diagnostic Tests Methods Group for bivariate meta-analysis models.58 Four input variables were used by Stata to perform the meta-analysis: the number of true positives, false positives, false negatives and true negatives for each study (the unit of analysis is the individual polyp). These were taken from our data extraction forms for each included study and included in a spreadsheet from which Stata directly drew the data. We also used Cochrane Review Manager (RevMan)59 to produce coupled forest plots of sensitivity and specificity and Summary Receiver Operating Curve (SROC) plots. The forest plots allow a visual interpretation of the individual study estimates, which can be informative in the assessment of heterogeneity. The SROC plots provide confidence and prediction regions around the summary estimate to enable joint inferences to be made about sensitivity and specificity. The confidence region is based on the confidence interval around the summary estimate. The prediction region indicated the area where we would expect results from a new study in the future to lie.52 In the SROC plots individual study estimate points are scaled to the sample size of the study (i.e. larger circles represent larger studies).

1. ASSESSMENT OF DIAGNOSTIC STUDIES
   1. Results
      1. Quantity and quality of research available

A total of 2068 references was identified by searches (after de-duplication) and two additional references were identified through other sources (Figure 4). We screened the titles and, where available, abstracts of the 2070 references and retrieved full copies of 125 references. We excluded 63 full text references, the majority either because the intervention (n=28) or comparator (n=29) did not meet the inclusion criteria (a list of the excluded studies with reasons for exclusion is presented in Appendix 4). Twenty-four references were designated as ‘Unclear’, all of which were conference abstracts (seven60-66 of these could be linked to full papers already either included or excluded and 17 appear to be ongoing or recently completed studies, see section ‎4.2). The remaining 32 references met the inclusion criteria of the systematic review and were included. These 32 references describe 30 separate studies.

The majority of the 30 studies that met the inclusion criteria for this systematic review evaluated NBI (n= 24) with 2 of these also evaluating one of the other interventions of interest (NBI & i-scan n=1; NBI & FICE n=1). A further 4 studies evaluated i-scan and a further 2 studies evaluated FICE. Thus the final tally of included evidence is as shown in Table 4.

References for retrieval and screening

n = 125

Titles and abstracts inspected n=2070

Total identified from database searching (after de-duplication)

n = 2068

Excluded n = 1945

Full papers excluded, n=63

Exclusion reasons:

Patient group n=1

Intervention n=28

Comparator n=29

Outcomes n=6

Design n=2

Abstract n=3

Studies described in our review n=30 (informed by 32 included references)

Additional records identified through other sources

n = 2

Unclear items n =24

(conference abstracts)

Figure Flow chart for the identification of studies

Table Evidence meeting the criteria for the systematic review

|  |  |
| --- | --- |
| **Interventions** | **Number of studies** |
| NBI | 221-6,8-14,67-77 |
| NBI & i-scan | 17 |
| NBI & FICE | 178 |
| i-scan | 479-82 |
| FICE | 283,84 |

***NBI***

Twenty-four studies1-14,67-78 included in the systematic review provided data on the use of NBI for virtual chromoendoscopy of colorectal polyps. From here on in the report Kaltenbach and colleagues5,73 and Gupta and colleagues69,74 will be identified by a single study reference to the main source of data (Kaltenbach and colleagues5 and Gupta and colleauges69). Two of these studies, a prospective cohort study by Lee and colleagues7 and an RCT by Kang and colleagues78 also reported on i-scan and FICE respectively and so are also included in our report in the i-scan and FICE sections.

An overview of the characteristics of the included NBI studies is presented in Table 5 (more detailed information is available in the data extraction forms presented in Appendix 3). More than half of the studies were conducted in the USA (14 studies1-3,5,6,10,12,13,67,69,70,75-77). Five studies were conducted in Europe (One in the UK,71 two studies in Italy,8,9 one in Italy and the Netherlands11 and one in Spain14). The remaining five studies were conducted in Asia: two in Japan4,72 and two in South Korea;7,78 and Australia.68 Seven of the studies focussed on diminutive polyps,3,5,7,8,68,69,77 nine focussed on small polyps (<10mm in size)1,4,9,11,14,71,72,76,78 and eight included polyps of any size.2,6,10,12,13,67,70,75 The studies that included polyps larger than diminutive polyps provided at least one outcome of interest for the sub-group of diminutive polyps. One study, by Hewett and colleagues 2012a2 restricted their study to polyps in the rectosigmoid colon.

Half of the studies enrolled participants undergoing colonoscopy either for screening, surveillance or because of symptoms 1,5,8-12,14,68,70,71,75 with all but two (Hewett and colleagues 2012b1 and Patel and colleagues3) reporting the proportions of participants in each category. Five studies enrolled participants undergoing colonoscopy for either screening or surveillance reasons2,7,69,76,77 but not because of symptoms, with one more study67 including participants presenting for elective screening or follow-up colonoscopy (reasons for the follow-up colonoscopy not provided). In two studies the entire sample of participants was drawn from a screening population72,78 In the remaining three studies the types of participants enrolled is not known because it was not reported in the publications.4,6,13

The male:female ratio of participants in the included studies lay between 1:1 and 2:1 in 13 studies,2,4,8-12,14,67,70,75-77 and between 2:1 and 3:1 in three studies.7,71,78 In the remaining four studies that reported the male:female ratio it was approximately 4:1,72 10:1,69 23:15 and the highest reported male:female ratio was 35:1.68 The male:female ratio of participants was not reported by four studies.1,3,6,13

The mean age of participants, if it was reported, lay between 54 years and 67 years (16 studies2,4,5,7-11,14,67,69,71,72,75,77,78) or the median age lay between 60 and 69 years (four studies12,68,70,76). The age of participants was not reported by the remaining four studies.1,3,6,13

The majority of the studies were conducted in a single centre,2,4,7-9,12-14,70,71,75-78 four were conducted in two centres,10,68,69,72 and one each at three centres,5 four centres3 and five centres.11 The number of centres was not reported by three studies.1,6,67

Study colonoscopies were undertaken by more than one endoscopist in most studies: one endoscopist in five studies,2,7,13,70,76 two in one study,1 three in one study,68 four in four studies,8,71,75,78 five in four studies,4,5,11,14 six in three studies,9,69,77 seven in three studies,12,67,72 10 in one study,10 12 in one study6 and the largest number of endoscopists was 26 in one study.3 In eight studies all the endoscopist(s) had prior experience of using NBI2,7-9,11,68,69,72 and in four studies some of the endoscopists had prior experience of using NBI.4,5,14,71 Only four studies stated that the endoscopists involved had no prior experience of using NBI to characterise colorectal polys3,6,10,78 but there were a further eight studies where it was not clear what experience of using NBI, if any, the endoscopist(s) may have had.1,12,13,67,70,75-77 The majority of the studies included an element of training for the endoscopist(s) in the characterisation of colorectal polyps using NBI, either training all endoscopists1,3,5,6,8-14,67,68,70,75,77,78 or the non-experts.71 In the study by Gupta and colleagues, which is a re-analysis of three earlier studies, training occurred in one of the three studies.69 There were five studies2,4,7,72,76 that did not state any training had taken place. In three of these, the endoscopists had prior experience of NBI.2,7,72 In the Iwatate and colleagues’ study4 the five endoscopists had mixed levels of NBI experience, and it was unclear what NBI experience the single endoscopist in the Shahid and colleagues’ study had.76

A variety of different systems were used to classify polyps as adenomas or hyperplastic polyps (Table 5). The most commonly used systems were the NICE classification scheme or a version of this which was cited by eight studies1,4-6,8,12,14,67 and the criteria proposed by Rex and colleagues13 which were cited by four studies.2,9,13,78 Two studies68,70 cited the Sano-Emura classification system, two75,76 based characterisations on modifications of the Kudo criteria and two3,69 on work by Rastogi and colleagues74,85-87 with one further study77 also citing a Rastogi and colleagues publication88 although it is not known in this case whether the criteria were the same. One study71 used vascular pattern intensity89 to classify polyps, one10 polyp colour, vessels and mucosal pattern90 and one7 the author’s own system. In the final two studies either criteria were reported by not attributed to any named system11 or no criteria were reported or cited.72

Table Overview of NBI studies

| **Study** | **Country** | **Centres** | **Patient populationa** | | | | **Patient characteristics** | | **NBI Processor** | **Endoscopists** | | | **Classification** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **n or n/Nb** | **SCR**  **(%)** | **SURV**  **(%)** | **SYM**  **(%)** | **Age, mean (SD) or median [range]c** | **sex (M/F %)** | **n** | **NBI experience** | **Training** |
| Aihara et al.67 | USA | NRd | NR/67 | Ye | NRe | NR | 54 (NR) | 64/36 | NR | 7 | Unclear | Yes | NICE-AS67 |
| Chandran et al.68 | Australia | 2 | 94 | 27 | 34 | 28 | 62 [19 to 84] | 97/3 | EXERA | 3 | Yes | Yes | Sano-Emura91 |
| Gupta et al.69 | USA | 2 | NR/410 | Y | Y | N | 62 (8)f | 90/10f | EXERA II | 6 | Yes | Yes (1/3 trials) | Author’s74,85,86 |
| Henry et al.70 | USA | 1 | NR/52 | 29f | 42f | 27f | 60 [34 to 84]f | 63/37f | EXERA II | 1 | Unclear | Yes | Sano-Emura91,92 |
| Hewett et al. 2012a2 | USA | 1 | 31/255 | 29f | 45f | NR | 60 (10)f | 52/48f | EXERA II | 1 | Yes | No | Rex et al. publication13 |
| Hewett et al. 2012b1 | USA | NR | NR/108 | Y | Y | Yg | NR | NR | EXERA II | 2 | Unclear | Yes | NICE – no reference cited |
| Ignjatovic et al.71 | UK | 1 | NR/130 | 25 | 63 | 12 | 63 (11)f | 67/33f | LUCERA | 4 | Mixed | Of non- experts | Vascular pattern intensity |
| Ikematsu et al.72 | Japan | 2 | NR/37 | 100 | No | No | 67 (NR)f | 76/24f | LUCERA | 7 | Yes | No | None stated |
| Iwatate et al.4 | Japan | 1 | NR/124 | NR | NR | NR | 56 (9)f | 58/42f | LUCERA | 5 | Mixed | No | NICE1,93 |
| Kaltenbach et al.5 | USA | 3 | NR/281 | 38f | 44f | 19f | 62 (9)f | 96/4f | EXERA II | 5 | Mixed | Yes | NICE1 |
| Kang et al.78 h | South Korea | 1 | 203/399 | 100 | N | N | 55 (9) | 68/32 | LUCERA | 4 | No | Yes | Polyp colour, vessels and surface pattern13,94,95 |
| Ladabaum et al.6 | USA | NR | NR | NR | NR | NR | NR | NR | EXERA II | 12 | No | Yes | NICE 96 |
| Lee et al.7 h | South Korea | 1 | 70/142 | Y | Y | N | 58 (11) | 74/26 | LUCERA | 1 | Yes | No | Author's |
| Paggi et al. 20158 | Italy | 1 | NR/284 | 43f | 28f | 30f | 61 (18)f | 63/37f | EXERA | 4 | Yes | Yes | Based on published criteria1 |
| Paggi et al. 20129 | Italy | 1 | 197/286 | 37f | 26f | 36f | 60 (16)f | 56/44f | EXERA | 6 | Yes | Yes | Simplified NBI criteria as proposed by Rex et al.13 |
| Patel et al.3 | USA | 4 | 451 | Y | Y | Y | NR | NR | EXERA II | 26 | No | Yes | Previously established NBI criteria74,86,87 |
| Pohl et al.10 | USA | 2 | 566/607 | 53i | 30i | 9i | 62 (8)i | 64/36i | NR | 10 | No | Yes | Polyp colour, vessels and mucosal pattern90 |
| Repici et al.11 | Italy and The Nether-lands | 5 | 212/278 | 37f | 27f | 36f | 63 (10)f | 58/42f | NR | 5 | Yes | Yes | Criteria reported, but not attributed to any named system |
| Rex et al.13 | USA | 1 | NR/136 | NR | NR | NR | NR | NR | EXERA HD 180 | 1 | Unclear | Yesj | Author's13 [also used by Hewett et al2] |
| Rogart et al.75 | USA | 1 | NR/131 | 55 | 24 | 15 | 59 (10) | 65/35 | EXERA II | 4 | Unclear (without extensive experience) | Yes | Simplified Kudo pit-pattern classification35 |
| Shahid et al.76 | USA | 1 | NR/65 | Y | Y | N | 69 [44 to 91]f | 62/38f | EXERA | 1 | Unclear | No | Kudo criteria as modified by Sano et al97 |
| Sola-Vera et al.14 | Spain | 1 | NR/195 | 38f | 16f | 25f | 64 (12)f | 56/44f | EXERA | 5 | 1/5 | Yes | NICE1,93 |
| Vu et al.77 | USA | 1 | 315 | 48 | 52 | N | 62 (9) | 51/49 | EXERA II | 6 | Unclear | Yes | Based on Rastogi88 |
| Wallace et al.12 | USA | 1 | NR/264 | 46 | 43f | 10f | 60 [33 to 85]f | 58/42f | EXERA II | 7 | Unclear | Yes | Simplified NICE6 |

NR, not reported; SCR - Screening; SURV - Surveillance; SYM - Symptomatic.

a If studies reported categories that appeared to fit under the ‘Screening’, ‘Surveillance’ or ‘Symptomatic’ headings these were grouped together. Some studies reported categories that did not fit under the ‘Screening’, ‘Surveillance’ or ‘Symptomatic’ headings or were described as ‘Other’ and these have not been reported. Percentages were rounded to whole numbers. Consequently the sum of percentages for some studies does not sum to 100%.

b The number of patients (n) for studies reporting only on diminutive polyps or the number of patients with diminutive polyps over the number of patients in the study overall (n/N) for studies reporting on diminutive polyps and larger polyps.

c Values rounded to the nearest whole number due to space limitations in the table.

d Number of centres not reported, however as all authors were affiliated to the same hospital, this is likely to have been a single centre study.

e Participants presented for elective screening or follow-up colonoscopy (reason for follow-up colonoscopy not reported).

f Results based on the total population and not available for the diminutive polyp subgroup (≤5 mm diminutive polyps)

g Described as ‘Diagnostic’

h Study included an arm that is included elsewhere in this report. Data reported here related only to the NBI arm of the study.

i Values based on 1100 participants who had a colonoscopy but at least one polyp was found in only 607 participants.

j This study contained an element not described as training by the study author but which the review team considered could be described as training.

The QUADAS assessments of the NBI studies indicates that the studies were at a low risk of spectrum, verification, disease progression, incorporation, test review, and clinical review biases (Table 6). Supporting information for the judgements shown in Table 6 is provided in the data extraction form for each study Appendix 3). Note that ‘Yes’ answers to QUADAS questions 1 to 9 (Table 3) imply a low risk of bias whereas ‘Yes’ answers to QUADAS questions 10 and 11 reflect adequacy of reporting and further supporting information is required to assess the risks of bias associated with these questions. For five studies3,4,6,13,67 the risk of spectrum bias (QUADAS question 1) was unclear because the reason(s) for patients having a colonoscopy were not reported. In two studies5,12 not all the polyps received verification by histopathology. In the Kaltenbach and colleagues’ study5 this was because when two or more non-neoplastic polyps were identified in the rectosigmoid colon in any one patient, a “representative sample” was resected for histopathological analysis. How often this circumstance arose was not reported. In the Wallace and colleagues’ study12 10 polyps (from 321 polyps, therefore representing 3% of the total) were not assessed by histopathology (and whether one further polyp had been assessed by histopathology was unclear). Overall it is our opinion that the risk of differential verification bias in these two studies was probably very low.

In all but four studies8,10,12,70 the risk of diagnostic review bias was judged to be low (QUADAS question 7) but was unclear in the studies by Henry and colleagues,70 Paggi and colleagues 2015,8 Pohl and colleagues10 and Wallace and colleagues12 because they did not report whether the histopathologist(s) were blinded to the NBI prediction for each polyp. The majority of studies did not report on uninterpretable/ intermediate test results probably because there were no uninterpretable/ intermediate test results due to the nature of the NBI assessments (studies typically required a decision to be made, although this could be assigned as low confidence in some studies). In the studies by Gupta and colleagues and Iwatate and colleagues there was evidence for uninterpretable or intermediate test results studies.4,69 An optical diagnosis could not be determined for four polyps (0.3%) in the study by Gupta and colleagues69 and Iwatate and colleagues4 excluded two patients with ‘unevaluable material’. Patel and colleagues3 reported that polyps were excluded from the analysis if a confidence level was not assigned or if histology was missing, “other”, or if the polyp could not be retrieved so it seems likely that there were also some uninterpretable or intermediate test results in this study. The outcome for QUADAS item 10 was judged unclear for the Wallace and colleagues’ study because not all patients who were randomised completed the study, so it is possible that uninterpretable test results were the reason for the missing data.

For the final QUADAS item (number 11, attrition bias) the judgement was ‘Yes’ for the majority of studies either because no withdrawals were apparent in the study1,2,4,7-9,13,14,67,68,70,72,75-77 or because withdrawals or other missing data were explained.5,10-12,71,78 For two studies the judgement was ‘Unclear’. In the Ladabaum and colleagues’ study6 this was because endoscopists were considered the subjects in the study and it was unclear whether any of them had dropped out of the study and because endoscopists were considered the subjects there was little reporting on those undergoing colonoscopy. In the Patel and colleagues’ study 3 the authors did not report the number of participants selected to take part or the number of patients included in the data analyses so it was unclear whether there had been any withdrawals. For one study, Gupta and colleagues69 this question was not applicable, because the included data were drawn from records of participants in three earlier trials that met the inclusion criteria for a retrospective analysis and therefore no participants were able to withdraw.

In addition to the assessment of the QUADAS items the generalisability of each study was also briefly summarised during data extraction (the summary of reviewers’ comments can be seen in full in the data extraction forms in Appendix 3). The overall impression from the included NBI studies is that they enrolled participants likely to be representative of the types of participants who would receive colonoscopy in the UK for screening, surveillance or on account of symptoms experienced (in line with the inclusion criteria for this systematic review). However, only one study was conducted in the UK, and just four elsewhere in Europe where it might reasonably be assumed that populations might be most similar to those in the UK. Most studies were conducted in a single centre so inherently these results may not be transferrable to other centres. In contrast, in most studies more than one endoscopist was involved in conducting colonoscopies and characterising polyps. Across all the studies a range of endoscopists was involved, some who were less experienced in conducting colonoscopy generally and had little or no experience using NBI through to very experienced endoscopists who also had extensive experience of using NBI. Training for endoscopists (which may have been to train those with no prior experience of NBI or to ensure that all endoscopists at a centre were characterising polyps to the same standard) formed a part of the majority of studies but how representative this training may have been to current UK practice is unknown. Finally a variety of classifications systems were used to determine whether polyps were adenomas or hyperplastic. The assessment group understands that, in countries such as the UK where polyp characterisation is conducted without magnification, the NICE classification is becoming widely accepted. It is unclear how generalisable the results obtained using other polyp classifications are to UK practice.

Table Overview of NBI QUADAS assessments

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **QUADAS ITEM (Questions are available in table footnotes)** | | | | | | | | | | |
| **Study** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** |
| Aihara et al.67 | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Chandran et al.68 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Gupta et al.69 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | n/a |
| Henry et al.70 | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | No | Yes |
| Hewett et al. 2012a2 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Hewett et al. 2012b1 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Ignjatovic et al.71 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Ikematsu et al.72 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Iwatate et al.4 | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Kaltenbach et al.5 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Kang et al.78 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Ladabaum et al.6 | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Unclear |
| Lee et al.7 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Paggi et al. 20158 | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | No | Yes |
| Paggi et al. 20129 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Patel et al.3 | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear |
| Pohl et al.10 | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | No | Yes |
| Repici et al.11 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Rex et al.13 | Unclear | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Rogart et al.75 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Shahid et al.76 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Sola-Vera et al.14 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Vu et al.77 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes |
| Wallace et al.12 | Yes | Yes | Yes | No | Yes | Yes | Unclear | Yes | Yes | Unclear | Yes |

Q1 Was the spectrum of patients representative of the patients who will receive the test in practice? Q2 Is the reference standard likely to classify the target condition correctly? Q3 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? Q4 Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? Q5 Did patients receive the same reference standard irrespective of the index test result? Q6 Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? Q7 Were the reference standard results interpreted without knowledge of the results of the index test? Q8 Were the index test results interpreted without knowledge of the results of the reference standard? Q9 Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? Q10 Were uninterpretable/ intermediate test results reported? Q11 Were withdrawals from the study explained?

***i-scan***

Five studies7,79-82 included in the systematic review provided data on the use of i-scan for virtual chromoendoscopy of colorectal polyps. An overview of the characteristics of the included i-scan studies is presented in Table 7 (more detailed information is available in the data extraction forms presented in Appendix 3). Four of the studies were conducted in Europe (Basford & colleagues in the UK,79 Hoffman and colleagues80 and Rath and colleagues82 in Germany, Pigo and colleagues81 in Italy) and one, Lee and colleagues,7 was conducted in South Korea. Basford & colleagues79 and Hoffman and colleagues80 enrolled all their participants from a screening population whereas the other three studies7,81,82 enrolled participants receiving colonoscopy for screening or surveillance purposes with one81 also including participants with gastrointestinal symptoms. In the three studies7,81,82 that enrolled different types of participants the proportions of participants receiving colonoscopy for screening, surveillance or symptoms was not reported. The Pigo and colleagues’ study81 enrolled almost equal proportions of men and women whereas more men than women were enrolled in the other four studies. Four studies7,80-82 reported the mean age of the participants which ranged from 55 years to 66 years. The two studies conducted in Germany80,82 did not report data on polyp characterisation for the whole colon, Hoffman and colleagues only reported on polyps in the last 30cm of colon and Rath and colleagues characterised polyps in the distal colon (decending colon, the sigmoid colon or the rectum). Three of the studies (Hoffman and colleagues,80 Lee and colleagues7 and Rath and colleagues82) focussed on the characterisation of diminutive polyps whereas Basford and colleagues79 focussed on small polyps (<10mm) and Pigo and colleagues81 included polyps of all sizes (and their data on diminutive polyps were limited to the rectosigmoid colon). Consequently, for the three studies that focussed on the characterisation of diminutive polyps, data are drawn from the whole patient population whereas it is not clear what proportion of the patients contributed data on diminutive polyp characterisation in the Basford and colleagues79and Pigo and colleagues81 studies. All the studies were conducted in single centres and, in all but one study, a single endoscopist performed the study colonoscopies and characterised polyps. In the Hoffman and colleagues’ study80 three endoscopists were involved. It was clearly reported in three of the five studies (Basford and colleagues,79 Hoffman and colleagues80 and Lee and colleagues7) that the endoscopist(s) had prior experience using i-scan but, due to an absence of reported details, it is not clear whether study endoscopists underwent any specific training with i-scan prior to the start of the studies. Only two studies7,82 used the same system, which was developed for the Lee and colleagues’ study,7 to classify polyps as adenomas or hyperplastic polyps (Table 7) the remainder all used different systems. One study81 cited the NICE classification system, one80 used surface pit pattern citing references of Kudo and colleagues among others, and Basford and colleagues79 developed their own system for their research.

The QUADAS assessments were conducted for each study and supporting information for the judgements shown in Table 8, is provided in the data extraction form for each study (Appendix 3). Note that ‘Yes’ answers to QUADAS questions 1 to 9 imply a low risk of bias whereas ‘Yes’ answers to QUADAS questions 10 and 11 reflect adequacy of reporting and further supporting information is required to assess the risks of bias associated with these questions. The QUADAS assessments of the i-scan studies indicate that the studies were at a low risk of spectrum, verification, disease progression, differential verification, incorporation, diagnostic review, test review, clinical review and test classification biases (Table 8). An exception is that, in the Hoffman and colleagues’ study,80 it was unclear how representative the patients were of those who would receive the test in practice because few details about the participants were reported, although it is known that they fulfilled the criteria for screening colonoscopy.

None of the studies indicated that there had been any uninterpretable or intermediate test results reported. Hoffman and colleagues80 reported results for normal mucosa in addition to adenomatous and hyperplastic polyps, but there is no indication in the paper that this was due to any difficulty in interpreting the index test.

No withdrawals (of patients or of polyps from the analysis) were apparent in the Hoffman and colleagues80 and Lee and colleagues7 studies. The exclusion of patients screened for inclusion but who were excluded from participation was explained by Basford and colleagues.79 Pigo and colleagues81 recruited 78 patients and 150 polyps were included in the analysis, but it was not clear whether the 150 polyps were from the full sample of 78 recruited participants. Rath and colleagues82 recruited 224 patients to their study but the analysis included only 77 of these (all were described as having distal diminutive polyps). It is possible that the remaining patients in these studies had larger-sized polyps located other than in the distal colon, but this is not explicitly stated. Therefore the Pigo and colleagues81 and the Rath and colleagues82 studies are at possible risk of attrition bias.

In addition to the assessment of the QUADAS items the generalisability of each study was also briefly summarised during data extraction (the summary of reviewer’s comments can be seen in full in the data extraction forms in Appendix 3). The overall impression from the included i-scan studies is they enrolled participants likely to be representative of the types of participants who would receive colonoscopy in the UK for screening or surveillance or on account of symptoms experienced. However, only one study was conducted in the UK, with three out of the remaining four conducted in Europe (two in Germany and one in Italy) whilst the final study was conducted in South Korea. Three of the five studies were conducted by endoscopists with prior experience of i-scan and all took place in single centres often described as academic or specialist centres. The results of these studies may therefore not be applicable to less experienced endoscopists working in more generalist or community settings. Only one study used the NICE classification system (which is becoming widely accepted for polyp characterisation without magnification) to determine whether polyps were adenomas or hyperplastic. It is unclear how generalisable the results obtained using other polyp classifications are to UK practice.

Table Overview of the i-scan studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Country** | **Centres** | **Patient population** | | | | **Patient** | | **Endoscopists** | | | **Classification** |
| **n** | **SCR** | **SURV** | **SYM** | **mean age, years (SD)** | **sex (% M:F)** | **n** | **i-scan experience** | **Training** |
| Basford et al.79 | UK | 1 | 84a | 100% | n/a | n/a | nrb | 65:35 | 1 | Yes | Unclearc | Developed by the endoscopist for this study. |
| Hoffman et al.80d | Germany | 1 | 69 | 100% | n/a | n/a | 55.9 | 62:38 | 3 | Yes | nr | Surface pit pattern |
| Lee et al.7e | South Korea | 1 | 72 | Yesf | Yesf | No | 55.4 (11.3) | 86:14 | 1 | Yes | nr | Developed by the endoscopist for this study. |
| Pigo et al.81g | Italy | 1 | 78a | Yesh | Yesh | Yesh | 52 (9) | 51:49 | 1 | nr | nr | NICE |
| Rath et al.82i | Germany | 1 | 77 | Yesf | Yesf | No | 65.5 (14.4) | 64:36 | 1 | nrj | nr | Used that developed by Lee 20117 |

NICE - NBI International Colorectal Endoscopic Classification; nr - not reported; SCR - Screening; SURV - Surveillance; SYM - Symptomatic

a The value of n reported is for the whole study because the number of participants with diminutive polyps was not reported separately. In Basford 2014 82% of the polyps were ≤ 5mm in size, in Pigo 58.7% of the polyps were ≤ 5mm in size

b Although the mean age was not reported the age range for the UK Bowel Screening Programme is 60-74 years.

c States that the endoscopist underwent a period of familiarisation with the endoscope and imaging technology which included developing the novel classification system used for the assessment of polyps by using i-scan during the study.

d This study allowed the optional use of magnification (level not stated) but the proportion of polyps characterised with the use of magnification was not reported. In addition the data on polyps only relates to the last 30cm of the colon.

e Lee 2011 also included an NBI arm which is reported in the earlier section on NBI and Table 5.

f The population is described as undergoing screening or surveillance colonoscopy but the proportions in each group are not stated.

g For diminutive polyps, data are only reported for rectosigmoid colon.

h The paper reports the number of participants for each of four indications for colonoscopy but it appears likely that participants could be included in more than one category because the totals sum to 87 but only 78 participants were included in the study. The indications for colonoscopy were: positivity for fecal occult blood test (51/78; 65.4%), polypectomy follow-up (20/78; 25.6%), gastrointestinal symptoms (7/78; 9.0%), and colorectal cancer familiarity (9/78; 11.5%).

i The focus of the study was characterisation of polyps in the distal colon (descending colon, the sigmoid colon, or the rectum).

j The endoscopist is described as experienced with no further details so it is not known whether the endoscopist had prior experience of i-scan.

Table Overview of i-scan QUADAS assessments

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **QUADAS ITEM** | | **Basford 201479** | **Hoffman 201080** | **Lee 2011a7** | **Pigo 201381** | **Rath 201582** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Yes | Unclear | Yes | Yes | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Yes | Yes | Yes | Yes | Yes |
| 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? | Yes | Yes | Yes | Yes | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Yes | Yes | Yes | Yes | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | Yes | Yes | Yes | Yes | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | Yes | Yes | Yes | Yes | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | Yes | Yes | Yes | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | Yes | Yes | Yes | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | Yes | Yes | Yes | Yes | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | No | No | No | No | No |
| 11 | Were withdrawals from the study explained? | Yes | Yes | Yes | Unclear | No |

a Note that this is duplicate information because Lee 20117 also contained an NBI arm and thus is also represented in the QUADAS table for NBI studies (Table 6).

**FICE**

Three studies included in the systematic review (Kang and colleagues;78 Longcroft-Wheaton and colleagues (2012);83 and Longcroft-Wheaton and colleagues (2011)84) provided data on the use of FICE for virtual chromoendoscopy of colorectal polyps (Table 9). Two of the studies were conducted in the UK83,84 and the other study was conducted in South Korea.78 In all three of these studies, all the included participants were undergoing colonoscopy for screening purposes. The Longcroft-Wheaton and colleagues (2012)83 study enrolled a slightly higher proportion of women than men, whereas the other two studies enrolled a higher proportion of men than women. All three studies reported the mean age of participants which ranged from 54 years78 to 65 years.84 All three studies focused on the real-time diagnosis of colorectal polyps sized <10mm, and provided sub-group analyses of diminutive polyps. All the studies were conducted in single centres. In the Kang and colleagues78 study, four endoscopists carried out the colonoscopies, while the other two studies each involved one endoscopist. Kang and colleagues78 reported that the study endoscopists had no prior experience with FICE, while Longcroft-Wheaton and colleagues (2012)83 and Longcroft-Wheaton and colleagues (2011)84 reported that the endoscopist in each of these studies had previous experience of in vivo diagnosis of polyps, although the authors did not specify endoscopists’ experience with FICE. Longcroft-Wheaton and colleagues (2012)83 stated that the study endoscopist had had prior training in real-time diagnosis. In the other studies,78,84 the endoscopists’ prior training in both real-time diagnosis and, more specifically, the use of FICE was unclear. Kang and colleagues78 noted however, that the endoscopists received feedback every two weeks during the study about the accuracy of their endoscopic predictions compared to the histopathological diagnosis. The study by Kang and colleagues78 (which also included an NBI arm) used a classification system for polyp characterisation based on colour, vascular density and vascular pattern.13,94,95,98 The two studies by Longcroft-Wheaton and colleagues83,84 both used a characterisation system based on vascular patterns which was developed by Teixeira and colleagues.99

Table 10 shows the quality assessments of the three FICE studies.78,83,84 Reviewers considered all three studies to be at a low risk of bias across most of the QUADAS items assessed. None of the studies, however, reported the number of uninterpretable test results, but reviewers believed this to be zero in two studies.78,84 Two studies explained participant withdrawals.78,83 Longcoft-Wheaton and colleagues (2011)84 did not state whether there were any withdrawals.

In addition to the assessment of the QUADAS items, the generalisability of each study was also briefly summarised during data extraction (the summary of reviewer’s comments can be seen in full in the data extraction forms in Appendix 3). Reviewers noted that two of the studies were conducted in the UK,83,84 and so are likely to be representative of a UK population (although it is noted that these studies included small numbers of participants – 50 and 89 participants each). It was also noted that it is unclear how representative participants in the South Korea study78 would be of the UK population and how similar the endoscopists’ training in this study would be to endoscopists’ training in the NHS in the UK. As all the studies were conducted in single centres it is unclear how the results would generalise to other centres and settings.

Table Overview of the FICE studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Country** | **Centres** | **Patient population** | | | | **Patient characteristics** | | **Endoscopists** | | | Classification system for polyp characterisation |
| n | SCR | SURV | SYM | age (mean) | sex (% M/F) | n | FICE experience | Training |
| Kang et al.a78 | South Korea | 1 | 196b | 100% | n/a | n/a | 54.3 (9.0) | 76:24 | 4 | No | Unclearc | Based on colour, vascular density & vascular pattern. Cites four references13,94,95,98 |
| Longcroft-Wheaton et al. 201283 | UK | 1 | 50b | 100% | n/a | n/a | 64 (4.2)d | 46:54e | 1 | Unclearf | Unclearf | Based on vascular patterns using a system developed by Teixeira et al.99 |
| Longcroft-Wheaton et al. 201184 | UK | 1 | 89b | 100% | n/a | n/a | 65 (6.7)g | 79:21g | 1 | Unclearf | Unclearf | System developed & validated by Teixeira et al.99 |

a Kang and colleagues also included an NBI arm which is reported in the earlier section on NBI and in Table 5

b Number is for the whole study (not just those patients with diminutive polyps). .

c States that the endoscopists performed a pilot study of a minimum of 50 examinations but it is not clear whether this was a minimum of 50 examinations each and whether the purpose of this study was to train the endoscopists.

d It is not clear whether this is the mean age for the 50 participants in this group with polyps or the total of 85 participants assigned to this group.

e This is the proportion of M:F for the total of 85 participants in the group. The proportion of M:F amongst the 50 participants with polyps is not reported.

f The endoscopist is described as trained and experienced in in vivo diagnostic methods but no further details are reported. It is not clear if FICE is the in vivo diagnostic method the endoscopist is trained and experienced in.

g For the total group of 89 participants (not just those with diminutive polyps)

Table Overview of QUADAS assessments for the FICE studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **QUADAS ITEM** | | **Kang 2015a** | **Longcroft-Wheaton 2012** | **Longcroft-Wheaton 2011** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Yes | Yes | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Yes | Yes | Yes |
| 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? | Yes | Yes | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Yes | Yes | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | Yes | Yes | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | Yes | Yes | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Yes | Yes | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes | Yes | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | Yes | Yes | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | No | No | No |
| 11 | Were withdrawals from the study explained? | Yes | Yes | No |

a Note that this is duplicate information because Kang 201578 also contained an NBI arm and thus is also represented in the QUADAS table for NBI studies (Table 6).

* + 1. Assessment of diagnostic accuracy (sensitivity, specificity, NPV, accuracy)

**NBI**

***Sensitivity and specificity of NBI for the characterisation of diminutive colorectal polyps***

All but one of the included NBI studies reported sensitivity75 or both sensitivity and specificity1-14,67-72,76,78 of NBI for the characterisation of diminutive colorectal polyps as adenomas or hyperplastic polyps as compared to the characterisation verified by histopathological assessment of the resected polyps. Only Vu and colleagues77 did not report on either sensitivity or specificity (this study was included in the systematic review because it reported accuracy in terms of the proportion of correctly classified polyps and data on surveillance intervals). The way in which data were reported by the studies varied and is shown in Table 11. Some studies reported on all the polyp characterisations made by study endoscopists. In other studies, the endoscopist indicated how confident they were in their NBI characterisation of the polyp as adenomatous or hyperplastic and results were reported separately for high and low confidence characterisations. Some studies reported data on all the characterisations and also the subsets of data for high and low confidence characterisations (data on low confidence characterisations is available in the data extraction forms in Appendix 3). One study, by Hewett and colleagues 2012a2 restricted their study to the rectosigmoid colon. As can be seen in Table 11 several other studies also reported data for sub-sections of the colon as well as for the whole colon. One study, Iwatate and colleagues4 reported a sub-group analysis by type of endoscopist (specialist or generalist).

The un-numbered sub-sections that follow Table 11 report on the:

* sensitivity and specificity of NBI for the characterisation of diminutive polyps in the whole colon (firstly data on all characterisations and then the separate subset of data on the polyp characterisations made with high confidence by the endoscopists) with accompanying meta-analyses (including a post-hoc analysis of high confidence characterisations made by endoscopists with prior experience of NBI).
* sensitivity and specificity of NBI for the characterisation of diminutive polyps in the rectosigmoid colon (again for all characterisations and separately for the subset of high confidence characterisations) with accompanying meta-analyses (including a post-hoc analysis of high confidence characterisations made by endoscopists with prior experience of NBI).
* sensitivity and specificity of NBI for the characterisation of polyps in parts of the colon other than the rectosigmoid colon (too few studies to meta-analyse).
* NPV of NBI for the characterisation of diminutive colorectal polyps; accuracy of NBI (proportion of correctly classified polyps).

Table Overview of the available data on sensitivity and specificity

|  |  |  |
| --- | --- | --- |
|  | **Reported data on all characterisations of polyps** | **Reported data on characterisations made with high confidence** |
| **Whole colon** | Aihara et al.67 (2x2 imputed)  Chandran et al.68  Gupta et al.69 (2x2 imputed)  Henry et al.70  Ignjatovic et al.71  Ikematsu et al.72 (2x2 imputed)  Iwatate et al.4  Kang et al.78 (2x2 imputed)  Ladabaum et al.6 (2x2 imputed)  Lee et al.7 (2x2 imputed)  Patel et al.a3 (2x2 imputed)  Repici et al.11 (2x2 imputed)  Rex et al.13 (2x2 imputed)  Rogart et al.b74 (unable to impute 2x2)  Shahid et al.76  Sola-Vera et al.14  Wallace et al.12 | Hewett et al. 2012bb,c 1 (unable to impute 2x2)  Iwatate et al.4  Kaltenbach et al.c 5 (2x2 imputed)  Ladabaum et al.b 6 (unable to impute 2x2)  Lee et al.7  Paggi et al. 2012c 9  Paggi et al. 2015c 8  Patel et al.a 3 (2x2 imputed)  Pohl et al.10  Repici et al.11 (2x2 imputed)  Rex et al.13  Sola-Vera et al.14  Wallace et al.12 |
| **Whole colon by colonosopist type** | Iwatate et al.4 (Specialist and generalist colonoscopists) |  |
| **Right colon** |  | Kaltenbach et al.5 (2x2 imputed) |
| **Proximal to splenic flexure** |  | Pohl et al.10 |
| **Left colon** | Gupta et al.69 (2x2 imputed) | Kaltenbach et al.5 (2x2 imputed) |
| **Distal colon** |  | Pohl et al.10 |
| **Rectosigmoid colon** | Hewett et al. 2012a 2 (2x2 imputed)  Ladabaum et al.6 (2x2 imputed)  Patel et al.b 3 (unable to impute 2x2)  Wallace et al.12 | Hewett et al. 2012a 2 (2x2 imputed)  Patel et al.b 3 (unable to impute 2x2)  Pohl et al.10  Repici et al.11 (2x2 imputed)  Wallace et al.12 |
| **Proximal to rectosigmoid colon** | Ladabaum et al.6 (2x2 imputed)  Patel et al.b 10 (unable to impute 2x2) | Patel et al.b 3 (unable to impute 2x2) |
| **Rectum** |  | Kaltenbach et al.5 (2x2 imputed) |

a Data to populate a 2x2 table were not reported and it proved difficult to impute data that would provide outcomes to match all the outcomes (accuracy, sensitivity, specificity, PPV & NPV) reported in the paper. Data imputed should be regarded as illustrative.

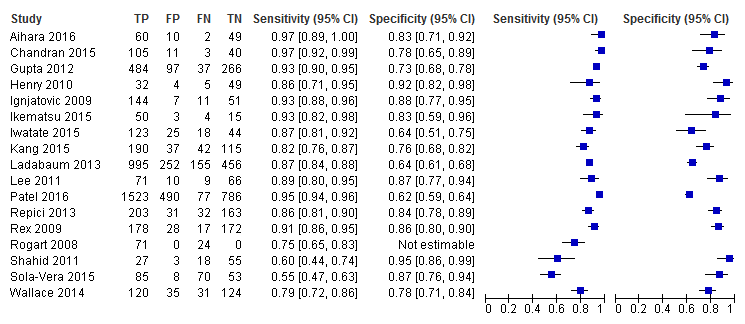
b Published papers reported values for sensitivity &/or specificity but data to populate a 2x2 table and recalculate these values were not reported or were reported incompletely and it was not possible to impute the missing data.

c Only reported outcomes for high confidence characterisations

***Sensitivity and specificity of NBI for the characterisation of diminutive colorectal polyps in the whole colon***

Twenty-two studies1,3-14,67-72,75,76,78 reported on the characterisation of diminutive polyps within the whole colon although five of these only reported data from high confidence characterisations.1,5,8-10

The results for all characterisations of diminutive polyps in the whole colon (i.e. not separated by confidence level), where 2x2 table data were reported or calculable, are shown in Figure 5.



a

a

a

a

a

a

a

a

a

b

a The values for the 2x2 tables of these studies were imputed. For Patel and colleagues values have been imputed by the reviewer but it was not possible to find a solution that agreed with all the 2x2 table outcomes reported in the paper. The imputed values for Patel and colleagues (which should be regarded as illustrative) produce the reported sensitivity and specificity, but produce values for PPV and NPV that are lower than reported and an accuracy value (proportion of correctly classified polyps among all the polyps) that is higher.

b Rogart and colleagues did not report a value for specificity and it was not possible to complete the 2x2 table from the information reported in the published paper.

Temporary reference list for this figure to be processed and removed in production:

Aihara et al.67

Chandran et al.68

Gupta et al.69

Henry et al.70

Ignjatovic et al.71

Ikematsu et al.72

Iwatate et al.4

Kang et al.78

Ladabaum et al.6

Lee et al.7

Patel et al.3

Repici et al.11

Rex et al.13

Rogart et al.74

Shahid et al.76

Sola-Vera et al.14

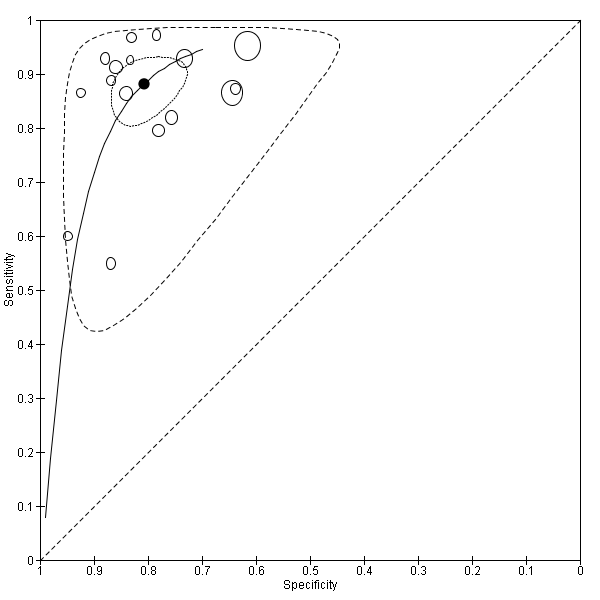
Wallace et al.12

Figure Accuracy of NBI for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps

The ability of NBI to correctly identify diminutive polyps as adenomas (i.e. the sensitivity of the test) ranged from 0.55 to 0.97 (i.e. 55% to 97%) across the 17 studies that reported this outcome. Sensitivity was above 90% in seven studies3,13,67-69,71,72 (and in two of these it was 95% or higher3,68), lay between 80% and 90% in six other studies4,6,7,11,70,78 and was below 80% in four studies.12,14,75,76

The ability of NBI to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) was typically lower than the sensitivity of the test, ranging from 0.62 to 0.95 (i.e. 62% to 95%) across the 16 studies that reported this outcome. Specificity was above 90% in just two studies,70,76 lay between 80% and 90% in seven studies7,11,13,14,67,71,72 and was below 80% in seven studies.3,4,6,12,68,69,78

It was possible to run a bivariate meta-analysis (using Stata/IC14 and metaandi57) for the 16 studies that reported both sensitivity and specificity. This produced a summary value for sensitivity of 0.88 (95% CI 0.83 to 0.92) and for specificity of 0.81 (95% CI 0.75 to 0.85). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 6. The 95% confidence region around the summary point indicates where we have 95% confidence that the summary point lies. The 95% prediction region illustrates the extent of statistical heterogeneity among the studies. If the bivariate model for sensitivity and specificity is correct, we have 95% confidence that the true sensitivity and specificity of a new study in the future will lie within the 95% prediction region. As can be observed from Figure 6 the 95% prediction region is large.



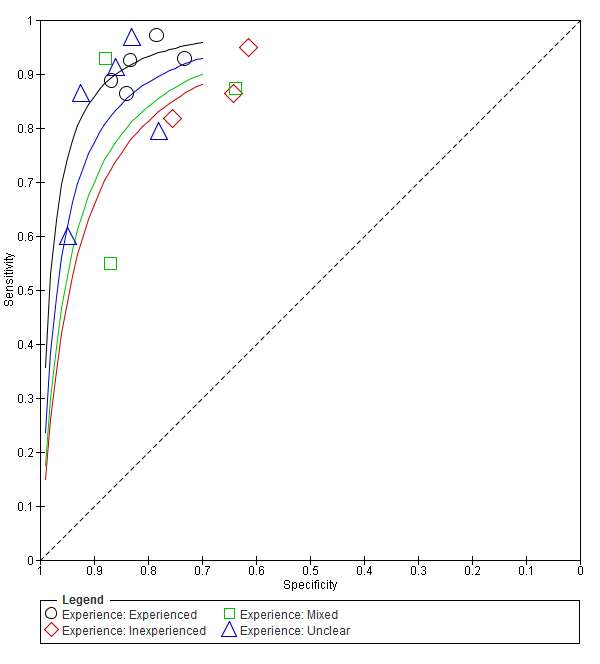
…..… 95% confidence region

95**%** prediction region

Summary point

Figure SROC plot from the meta-analysis of NBI for all characterisations of polyps in the whole colon.

In order to investigate the heterogeneity between studies, a covariate for endoscopist experience with NBI was added to RevMan and separate SROC curves were drawn as shown in Figure 7. Whilst caution must be taken when interpreting this figure due to the small number of studies for each subgroup, it nevertheless appears to support the hypothesis that endoscopists with prior experience of using NBI to characterise diminutive colorectal polyps achieve higher sensitivity and specificity than endoscopists who have had no prior experience of using NBI to characterise diminutive colorectal polyps (other than any training that they undertook at the start of the study).



Experienced

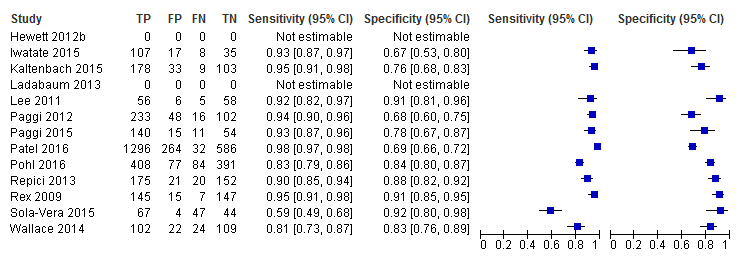
Experience unclear

Mixed experience

Inexperienced

Figure SROC plots for all characterisations of polyps in the whole colon by endoscopists level of experience using NBI

Results for studies that reported results from polyp characterisations using NBI that were designated as high confidence decisions, and where 2x2 table data were reported or calculable, are shown in Figure 8.



b

b

b

a

a

a It was not possible for us to impute the 2x2 table data necessary to plot these results within this figure. Hewett and colleagues’ study 2012b1 reported a value for sensitivity of 98% (no confidence interval provided and specificity not reported) and Ladabaum and colleagues’6 reported sensitivity of 88.4% (95% CI 82.2 to 94.7) and specificity of 44.1% (26.5 to 61.6).

b The values for the 2x2 tables of these studies were imputed.

Temporary reference list for this figure to be processed and removed in production:

Hewett et al. 2012b1

Iwatate et al.4

Kaltenbach et al.5

Ladabaum et al.6

Lee et al.7

Paggi et al. 20129

Paggi et al. 20158

Patel et al.3

Pohl et al.10

Repici et al.11

Rex et al.13

Sola-Vera et al.14

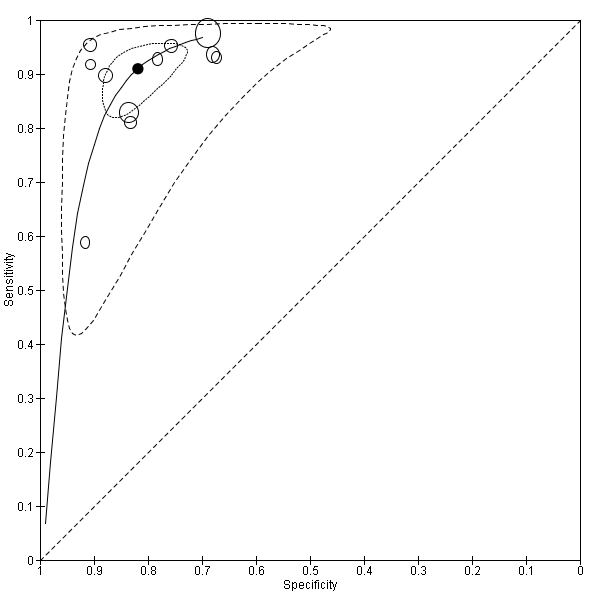
Wallace et al.12

Figure Accuracy of NBI high confidence decisions for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps in the whole colon

The ability of high confidence characterisations made with NBI to correctly identify diminutive polyps as adenomas (ie. the sensitivity of the test) was 0.90 or more (i.e. 90% or more) in nine of the 13 studies1,3-5,7-9,11,13 (in four of these it was 95% or higher1,3,5,13) and it lay between 80% and 90% in three other studies.6,10,12 The lowest sensitivity value reported was 59% by Sola-Vera and colleagues.14 Some studies reported the sensitivity obtained from all characterisations and the sensitivity from only the high confidence characterisations. In each study where both these values were reported, the sensitivity was higher when obtained from high confidence decisions (difference ranging from an increase of 1.5% to 5.8%).

The ability of NBI to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) from high confidence polyp characterisations was just above 90% (i.e. above 0.90) in three studies7,13,14 but did not exceed 92% in any study. In just three studies specificity lay between 80% and 90%10-12 but in the majority of the studies it lay below 80%3-6,8,9 with the lowest specificity just 44.1% reported by Ladabaum and colleagues.6 Specificity was higher when obtained from high confidence decisions in seven of the eight studies that reported both the specificity obtained from all characterisations and the specificity from only the high confidence characterisations, with the increase ranging from 3.5% to 7.3%. The one exception was the study by Ladabaum and colleagues6 where the specificity calculated from high confidence characterisations was lower than that obtained from all characterisations (44.1% versus 64.4% respectively).

A bivariate meta-analysis (using Stata/IC14 and metaandi57) was run for the 11 studies that reported both sensitivity and specificity from polyp characterisations made with high confidence. This produced a summary value for sensitivity of 0.91 (95% CI 0.85 to 0.95) and for specificity of 0.82 (95% CI 0.76 to 0.87). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 9. The effect of reporting only on high confidence characterisations in comparison to all polyp characterisations is to move the summary estimate up (increasing sensitivity) and slightly to the left (increasing specificity).



…..… 95% confidence region

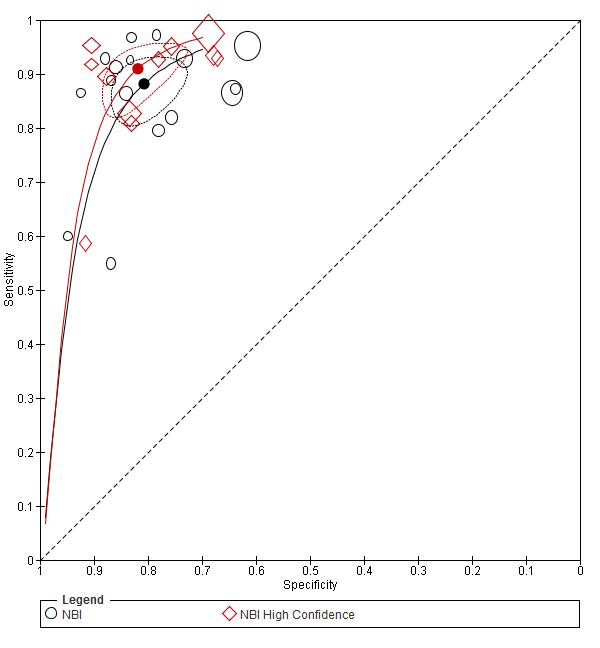
95**%** prediction region

Summary point

Note that two studies were not included in the meta-analysis: Hewett and colleagues’ study 2012b1 sensitivity 98%; Ladabaum and colleagues’6 sensitivity 88.4% (95% CI 82.2 to 94.7), specificity 44.1% (26.5 to 61.6).

Figure SROC plot showing the summary point on the summary curve from the meta-analysis of NBI for high confidence characterisations of polyps in the whole colon

The impact of restricting the analysis to high confidence characterisations in comparison to including all characterisations can be observed in Figure 10 in which shows both summary curves on the same plot. As already stated the effect of reporting only on high confidence characterisations in comparison to all polyp characterisations is that the summary estimate moves up (increasing sensitivity) and slightly to the left (increasing specificity).



…..… 95% confidence region

Summary point

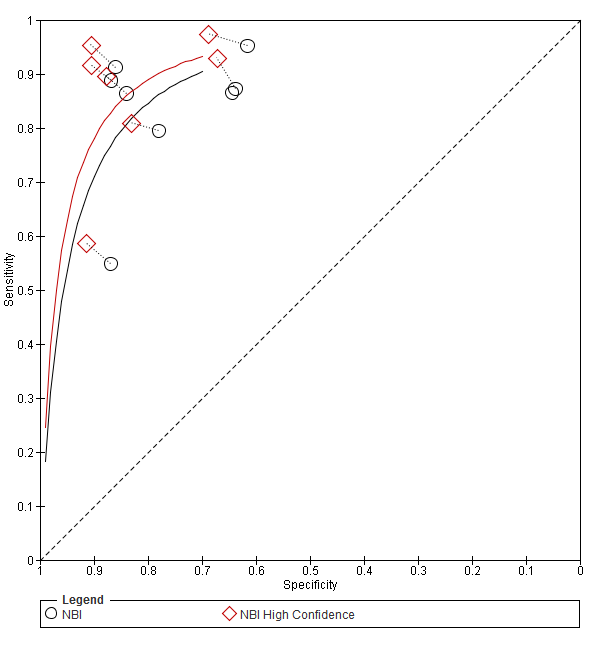
NBI

NBI High Confidence

Note: for clarity the 95% prediction regions are not shown on this plot

Figure SROC for all NBI characterisations of polyps in the whole colon and SROC for only high confidence NBI characterisations of polyps in the whole colon shown on the same plot

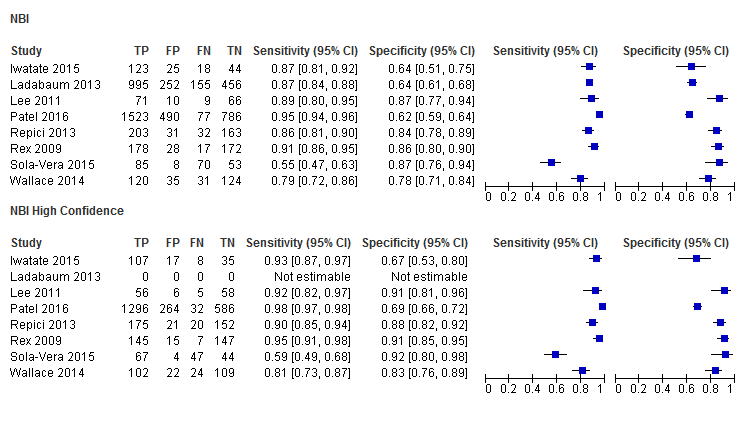
Seven studies3,4,6,7,11-14 reported both sensitivity and specificity from all diminutive polyp characterisations and separately for only high confidence diminutive polyp characterisations, although for one of the these studies6 2x2 table data were not available for the high confidence characterisations [which had a reported sensitivity of 88.4% (95% CI 82.2 to 94.7) and specificity of 44.1% (26.5 to 61.6)]. The pairs of results from these studies are shown in Figure 11 and forest plots in Figure 12.



NBI

NBI High Confidence

Figure Plot showing paired data from the studies that reported on all diminutive polyp characterisations and separately on high confidence diminutive polyp characterisations



a

a

a

a

a

a

a

a

b

a The values for the 2x2 tables of these studies were imputed

b It was not possible for us to impute the 2x2 table data necessary to plot these results within this figure [reported sensitivity of 88.4% (95% CI 82.2 to 94.7) and specificity of 44.1% (26.5 to 61.6)]

Temporary reference list for this figure to be processed and removed in production:

Iwatate et al.4

Ladabaum et al.6

Lee et al.7

Patel et al.3

Repici et al.11

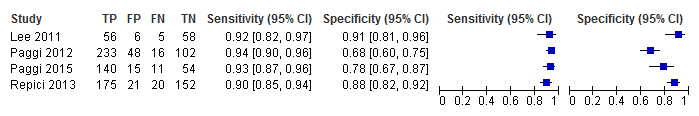
Rex et al.13

Sola-Vera et al.14

Wallace et al.12

Figure Accuracy of NBI in studies that reported on all diminutive polyp characterisations and separately on high confidence diminutive polyp characterisations

To obtain data for a scenario analysis within the economic model (section ‎5.5.2.2) a post-hoc bivariate meta-analysis (using Stata/IC14 and metaandi57) was run for a subgroup in which endoscopists experienced in the use of NBI characterised the polyps in the whole colon (Figure 13). There were four such studies included in this analysis.7-9,11



a

a The values for the 2x2 table of this study were imputedTemporary reference list for this figure to be processed and removed in production:

Lee et al.7

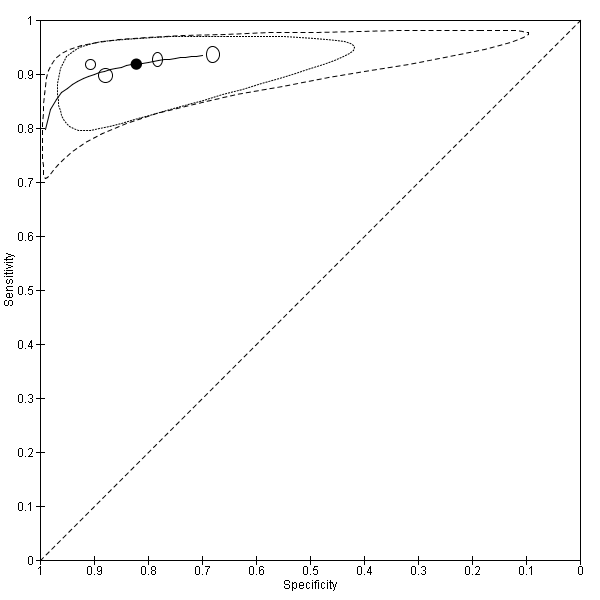
Paggi et al. 20129

Paggi et al. 20158

Repici et al.11

Figure Accuracy of NBI high confidence decisions for characterising diminutive colorectal polyps in the whole colon as either adenomas or hyperplastic polyps when made by endoscopists experienced in the use of NBI

The meta-analysis produced a summary value for sensitivity of 0.92 (95% CI 0.89 to 0.94) and for specificity of 0.82 (95% CI 0.72 to 0.89). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 14. Restricting the meta-analysis from 11 studies reporting different levels of NBI experience (Experienced n=4; Mixed experience n=3; Inexperienced n=2; Unclear n=2) to the four studies that reported endoscopists experienced in the use of NBI narrowed the 95% CI for sensitivity [11 studies variety of experience: 0.91 (95% CI 0.85 to 0.95); four studies with prior NBI experience: 0.91 (95% CI 0.89 to 0.94)] and widened the 95% CI for specificity [11 studies variety of experience: 0.82 (95% CI 0.76 to 0.87); four studies with prior NBI experience: 0.82 (95% CI 0.72 to 0.89). The changes in the 95% confidence intervals are reflected in the change in the size and shape of the 95% confidence region and 95% prediction region in Figure 14 in comparison to Figure 9.



…..… 95% confidence region

95**%** prediction region

Summary point

Figure SROC plot showing the summary point on the summary curve from the meta-analysis of NBI for high confidence characterisations of polyps in the whole colon when made by endoscopists experienced in the use of NBI

Colonoscopies in one study, by Iwatate and colleagues4 were conducted by five endoscopists. Two of the five endoscopists were described as specialists in colonoscopy and they had extensive experience in magnifying colonoscopy with NBI (>1000 cases). The other three endoscopists were described as general endoscopists with limited experience in magnifying colonoscopy with NBI (≤1000 cases). As shown in Table 12 the two specialist endoscopists achieved higher sensitivity and specificity than the three general endoscopists but the difference between the two was only statistically significant for specificity (p=0.007).

Table Sensitivity and specificity according to experience with NBI of the endoscopists

|  |  |  |
| --- | --- | --- |
|  | **High confidence characterisations of polyps 1-5mm** | |
| Specialist endoscopists | General endoscopists |
| - Sensitivity | 93.5% | 92.9% |
| 95% CI | 78.58% to 99.21% a | 85.10% to 97.33% a |
| - Specificity | 87.0%1 | 51.7%1 |
| 95% CI | 66.41% to 97.22% a | 32.53% to 70.55% a |

\* calculated by reviewer

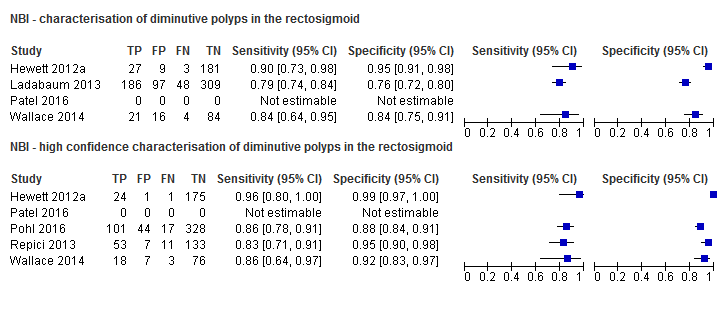
1 The differences between the specificity rates for the SC and the GE group were significant p=0.007.

***Sensitivity and specificity of NBI for the characterisation of diminutive colorectal polyps in the rectosigmoid colon.***

As shown in Table 11 four studies2,3,6,12 reported sensitivity and specificity following characterisation (any level of confidence) of diminutive polyps in the rectosigmoid colon with three of these reporting sufficient data for a 2x2 table to be constructed for entry into meta-analysis.2,6,12

Three of the four studies2,3,12 that reported results for all characterisations also reported sensitivity and specificity following high confidence characterisations of polyps in the rectosigmoid colon with two further studies10,11 only reporting high confidence characterisation data. Four of the five studies reporting on high confidence characterisations provided sufficient data for 2x2 tables to be constructed for entry into meta-analysis.2,10-12

Results from the studies that used NBI to characterise polyps in the rectosigmoid colon, where 2x2 table data were reported or calculable, are shown in Figure 15. The results from Patel and colleagues3 are not represented in Figure 15 because it was not possible to impute values into a 2x2 table that provided a solution for the reported outcomes in the paper (accuracy, sensitivity, specificity, PPV and NPV).



b

b

a

a

a

a The values for the 2x2 tables of these studies were imputed

b It was not possible for us to impute the 2x2 table data necessary to plot these results within this figure. For characterisation of all diminutive polyps in the rectosigmoid colon Patel and colleagues3 reported sensitivity of 88.4% (95% CI 84.8% to 92.0%) and specificity of 78.3% (95% CI 71.8% to 84.9%). The high confidence polyp characterisations yielded sensitivity of 90.9% (95% CI 87.4% to 94.4%) and specificity of 88.6% (95% CI 81.0% to 96.1%).

Temporary reference list for this figure to be processed and removed in production:

Top panel: Hewett et al. 2012a 2

Ladabaum et al.6

Patel et al.3

Wallace et al.12

Bottom panel: Hewett et al. 2012a2

Patel et al.3

Pohl et al.10

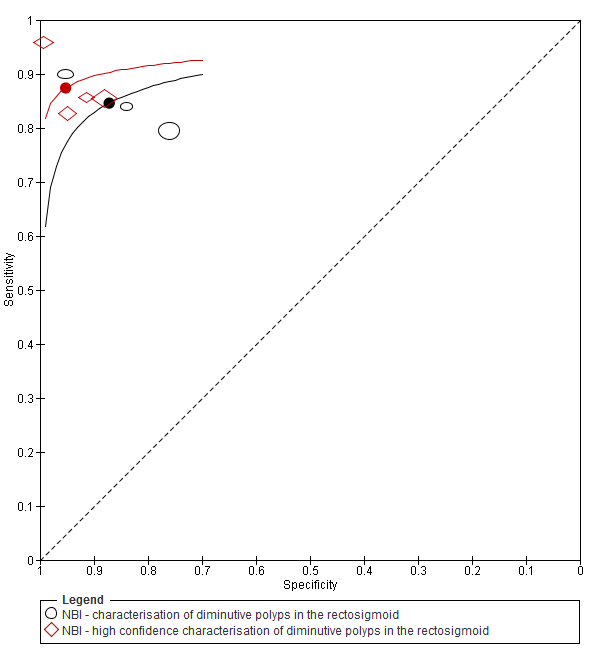
Repici et al.11

Wallace et al.12

Figure Accuracy of NBI for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps in the rectosigmoid colon

a

Bivariate meta-analyses was conducted (using Stata/IC14 and xtmelogit or using Stata/IC14 and metandi57) of the studies where 2x2 table data were available. For all characterisations of diminutive polyps in the rectosigmoid colon the summary value for sensitivity is 0.85 (95% CI 0.75 to 0.91) and for specificity is 0.87 (95% CI 0.74 to 0.94). For high confidence characterisations of diminutive polyps in the rectosigmoid colon the summary value for sensitivity is 0.87 (95% CI 0.80, 0.92) and for specificity is 0.95 (95% CI 0.87, 0.98). The parameter estimates for the bivariate model from these two meta-analyses were entered into RevMan to produce the SROC plot shown below in Figure 16. As seen with the results for the whole colon, the effect of reporting only high confidence polyp characterisations in comparison to all polyp characterisations is to increase sensitivity and specificity (summary point moves up and to the left on the SROC plot).



Summary points

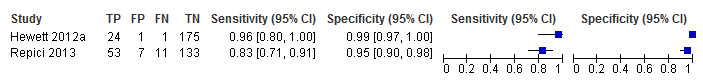
High confidence rectosigmoid colon

All characterisations rectosigmoid colon

Note that one study was not included in either meta-analysis: Patel and colleagues3 all characterisations sensitivity 88.4% (95% CI 84.8% to 92.0%), specificity 78.3% (95% CI 71.8% to 84.9%); high confidence characterisations sensitivity 90.9% (95% CI 87.4% to 94.4%), specificity 88.6% (95% CI 81.0% to 96.1%). The large 95% confidence and a 95% prediction regions which were generated for the high confidence characterisation plot are not shown on this figure and the software used to draw the SROC plot (Review Manager 5.3) did not generate a 95% confidence region or a 95% prediction region for the other data set.

Figure SROC plot showing the summary points on the summary curves from the meta-analyses of NBI for all characterisations of polyps and for only high confidence characterisations of polyps in the rectosigmoid colon

To obtain data for a scenario analysis within the economic model (section ‎5.5.2.2) a post-hoc bivariate meta-analysis (using Stata/IC14 and xtmelogit) was run for a sub-group of studies in which the endoscopists were experienced in the use of NBI. There were two such studies2,11 included in the analysis (Figure 17).



a

a

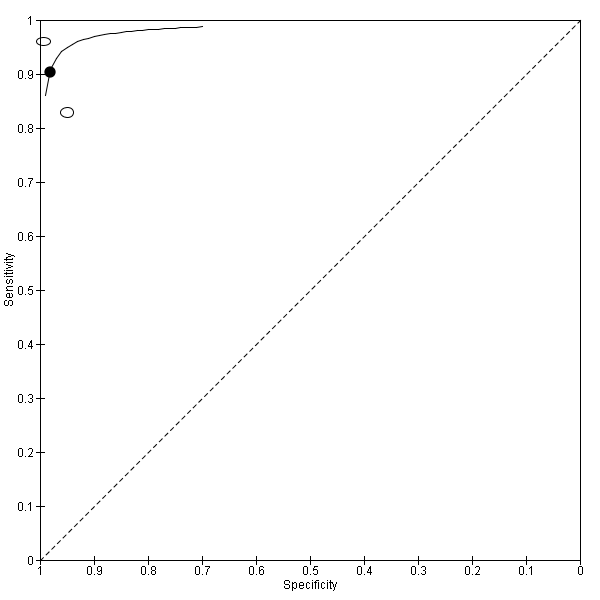
a The values for the 2x2 tables of these studies were imputed

Temporary reference list for this figure to be processed and removed in production:

Hewett et al. 2012a2

Repici et al.11Figure Accuracy of NBI high confidence decisions, made by endoscopists with prior experience of NBI, for characterising diminutive colorectal polyps in the rectosigmoid colon as either adenomas or hyperplastic polyps

The meta-analysis produced a summary value for sensitivity of 0.90 (95% CI 0.71 to 0.97) and for specificity of 0.98 (95% CI 0.91 to 1.00). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 18. Restricting the meta-analysis from the four studies reporting different levels of NBI experience (Experienced n=2; Inexperienced n=1; Unclear n=1) to only the two studies where endoscopists had experience in the use of NBI increased the summary value for sensitivity whilst widening the 95% CI [four studies variety of experience: 0.87 (95% CI 0.80, 0.92); two studies with prior NBI experience: 0.90 (95% CI 0.71 to 0.97)] and increased the summary value for specificity whilst narrowing the 95% CI [four studies variety of experience: 0.95 (95% CI 0.87, 0.98); two studies with prior NBI experience: 0.98 (95% CI 0.91 to 1.00).



Note that the software used to draw the SROC plot (Review Manager 5.3) did not generate a 95% confidence region or a 95% prediction region for this meta-analysis. It is presumed that this is because of the small number of studies.

Figure SROC plot showing the summary point on the summary curve from the meta-analyses of NBI for high confidence characterisations of polyps in the rectosigmoid colon made by endoscopists with prior experience of NBI

***Sensitivity and specificity of NBI for the characterisation of diminutive colorectal polyps in parts of the colon other than the rectosigmoid colon***

Five studies3,5,6,10,69 provided data on the characterisation of diminutive polyps in regions of the colon, other than the rectosigmoid colon (Table 11). The results reported by these studies are summarised in Table 13

Table Summary of the sensitivity and specificity of NBI for the characterisation of diminutive colorectal polyps in parts of the colon other than the rectosigmoid colon

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Study** | **Sensitivity** | **95% CI** | **Specificity** | **95% CI** |
| **Right colon** | | | | | |
| High confidence characterisations | Kaltenbach et al.5 | 96.4% | 91.0% to 99.0% | 61.4% | 45.5% to 75.6% |
| **Proximal to splenic flexure** | | | | | |
| High confidence characterisations | Pohl et al.10 | 82% | 77.8% to 86.4% | 62% | 49.8% to 73.7% |
| **Left colon** | | | | | |
| All characterisations of polyps | Gupta et al.69 | 91.4% | 86.8% to 94.8% | 78.1% | 73.0% to 82.6% |
| High confidence characterisations | Kaltenbach et al.5 | 95.5% | 87.5% to 99.1% | 83.6% | 71.2% to 92.2% |
| **Distal colon** |  |  |  |  |  |
| High confidence characterisations | Pohl et al.10 | 84% | 77.6% to 89.0% | 87% | 83.5% to 90.3% |
| **Proximal to rectosigmoid colon** | | | | | |
| All characterisations of polyps | Ladabaum et al.6 | 88.2 | 82.2% to 94.2% | 49.7 | 34.7% to 64.6% |
| Patel et al.3 | 91.0% | 88.3% to 94.0% | 36.9% | 27.7% to 46.1% |
| High confidence characterisations | Patel et al.3 | 96.2% | 94.1% to 98.4% | 34.9% | 22.1% to 47.7% |
| Patel et al.3 | 73.7% | 65.8% to 81.5% | 44.4% | 37.3% to 51.1% |
| **Rectum** |  |  |  |  |  |
| High confidence characterisations | Kaltenbach et al.5 | 77.8% | 40.0% to 97.2% | 81.1% | 64.8% to 92.0% |

***Negative predictive value of NBI for the characterisation of diminutive colorectal polyps***

The negative predictive value is the probability that subjects with a negative screening test (i.e. colorectal polyp is characterised as hyperplastic) truly do not have an adenoma. However, it must be borne in mind when viewing these results that the negative predictive value is influenced by the prevalence of disease (i.e. in this case the prevalence of adenomas in the tested populations). When prevalence is increased the result is a decrease in the negative predictive value. Due to the importance of NPV within the PIVI statement (see section ‎1.3.1) consideration was given to meta-analysing NPVs from the included studies even though this is not advised by either the NICE Diagnostics Programme Manual49 or the Cochrane Diagnostic Test Accuracy Handbook.48 However, because it is clear that the prevalence of adenomas and hyperplastic polyps is likely to vary between studies [e.g. due to differences in case mix (screening, surveillance and symptomatic populations) and patient characteristics (age, sex)] we chose not to pool NPV values across studies. Instead we have provided forest plots for these outcomes and marked the 90% threshold value on each plot.

For the characterisations of diminutive polyps in the whole colon (made with any level of confidence) the NPV ranged from 43% to 96.1% (Figure 19 and Table 14). The study by Sola-Vera and colleagues14 is noteworthy because this study reported the lowest NPV and it was far lower than in any other study. All the other studies reported NPV values over 70% with five studies reporting NPV values of 90% or more,3,13,67,68,70 however it should be noted that the lower limit of the 95% confidence interval fell below 90% in every study except Patel and colleagues.3

Limiting the assessment of NPV to high confidence polyp characterisations increased the NPV which ranged from 48% to 98.3% in the studies that reported this outcome (Table 14 and Figure 20). Again the study by Sola-Vera and colleagues had the lowest NPV of any study by a considerable margin. All the other studies reported NPV values for high confidence assessments of over 78% with five studies reporting NPV values of 90% or more.1,3,5,7,13 Once again however, inspection of the 95% confidence intervals reveals that the lower limit of this fell below 90% in all but two studies.3,13

One study, by Iwatate and colleagues,4 compared differences in NPV achieved by specialists in colonoscopy and general endoscopists. Specialists in colonoscopy achieved NPVs of over 90% (mean value 90.9%, 95% CI 70.8 to 98.9) whereas the NPVs achieved by general endoscopists were lower with a mean value of 71.4% (95% CI 47.8 to 88.8), however the difference between the groups was not statistically significant.

Aihara 201667

Chandran 201568

Gupta 201269

Henry 201070

Ignjatovic 200971

Ikematsu 201572

Iwatate 20154

Kang 201578

Ladabaum 20136

Lee 20117

Patel 20163

Repici 201311

Rex 200913

Shahid 201176

Sola-Vera 201514

Wallace 201412

Figure NPV of NBI for all characterisations of diminutive polyps in the whole colon (made with any level of confidence)

Table Negative predictive value of NBI for the characterisation of diminutive polyps in the whole colon

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All characterisations** | | **High confidence characterisations** | |
|  | **Value** | **95% CI** | **Value** | **95% CI** |
| **Diminutive polyps whole colon** | | | | |
| Aihara et al.67 | 96.1% | 85.4% to 99.3% | nr | nr |
| Chandran et al.68 | 93% | 80.9% to 98.5% | nr | nr |
| Gupta et al.69 | 87.8% a | 83.6% to 91.3% a | nr | nr |
| Henry et al.70 | 90.7% | 79% to 97% | nr | nr |
| Hewett et al. 2012b1 | nr | nr | 95% | nr |
| Ignjatovic et al.71 | 82.3 % a | 70.5% to 90.8% a | nr | nr |
| Ikematsu et al.72 | 78.9% | 54.4% to 94.0% a | nr | nr |
| Iwatate et al.4 | 71.0% | 58.1% to 81.8% a | 81.4% | 66.6% to 91.6% a |
| Kaltenbach et al.5 | nr | nr | 92.0% | 85.3% to 96.3% |
| Kang et al.78 | 73.2% | 66.6% to 80.5% | nr | nr |
| Ladabaum et al.6 | 75.9% | 69.1% to 82.7% | 78.3% | 69.6% to 87.0% |
| Lee et al.7 | 88.0% | 80.6% to 95.4% | 92.1% a | 82.4% to 97.4% a |
| Paggi et al. 20158 | nr | nr | 83.1 % a | 71.7% to 91.2% a |
| Paggi et al. 20129 | nr | nr | 86.4% a | 78.9% to 92.1%  a |
| Patel et al.3 | 94.2% | 90.4% to 98.0% | 98.3% | 95.7% to 100.0% |
| Pohl et al.10 | nr | nr | 82.3 | 78.6% to 85.6% |
| Repici et al.11 | 84% | 78% - 88% | 89% | 84% to 93% |
| Rex et al.13 | 91.0 % a | 86.0% to 94.7% a | 95.5 % a | 90.9% to 98.2% a |
| Rogart et al.75 | nr | nr | nr | nr |
| Shahid et al.76 | 75% | 62% to 84% | nr | nr |
| Sola-Vera et al.14 | 43% | 34% to 52% | 48% | 37% to 59% |
| Vu et al.77 | nr | nr | nr | nr |
| Wallace et al.12 | 80% | 72.8% to 86.0% a | 82% | 74.4% to 88.1% a |
| **Assessed by specialists in colonoscopy (whole colon)** | | | | |
| Iwatate et al.4 | nr | nr | 90.9% | 70.8% to 98.9% a |
| **Assessed by general endoscopists (whole colon)** | | | | |
| Iwatate et al.4 | nr | nr | 71.4% | 47.8% to 88.7% a |

a Calculated by reviewer

Hewett 2012b1

Iwatate 20154

Kaltenbach 20155

Ladabaum 20136

Lee 20117

Paggi 20158

Paggi 20129

Patel 20163

Pohl 201610

Repici 201311

Rex 200913

Sola-Vera 201514

Wallace 201412

Note that no 95% confidence interval was reported for the Hewett 2012b study.1

Figure NPV of NBI for high confidence characterisations of diminutive polyps in the whole colon

Seven studies2,3,6,10-12,69 reported on the NPV for the characterisation of diminutive polyps in the rectosigmoid colon (top section Table 15). Five of these studies2,3,6,12,69 reported data for all diminutive polyp characterisations in the rectosigmoid colon and NPV ranged from 87.4% to 98.4%. In four2,3,12,69 of these five studies NPV was over 90%. Only in the study by Ladabaum and colleagues,6 was the 90% threshold not reached.

Data for high confidence characterisations of polyps in the rectosigmoid colon were reported by five of the seven studies (Figure 21).2,3,10-12 In three of these five studies2,3,12 the data on high confidence characterisations were provided in addition to data on all polyp characterisations in the rectosigmoid colon. In these studies the high confidence results led to NPVs that remained at over 90% and were slightly increased. Two studies10,11 provided only high confidence results for the rectosigmoid colon and in both the NPV was over the 90% threshold. It is worth noting however that in two11,12 of the five studies that report NPV for high confidence characterisations of diminutive polyps in the rectosigmoid colon, the lower limit of the 95% confidence interval falls below 90%.

Hewett 2012a2

Patel 20163

Pohl 201610

Repici 201311

Wallace 201412

Figure NPV of NBI for high confidence characterisations of diminutive polyps in the rectosigmoid colon

The NPV of NBI for characterisation of diminutive polyps in other regions of the colon (where reported by studies) is also presented in Table 15. Although the mean NPV was above the 90% threshold in some instances none of the lower limits of the 95% confidence interval lay above 90%.

One study10 reported the NPV for characterisations of diminutive polyps in the rectosigmoid colon achieved by endoscopists with prior optical diagnosis experience in colonoscopy and by endoscopists without prior optical diagnosis experience. Endoscopists with prior optical diagnosis experience achieved an NPV of 96.6% (95% CI 92.7% to 98.7%) whereas the NPV achieved by endoscopists without prior optical diagnosis experience was lower at 93.5% (95% CI 88.7% to 96.7%).

Table Negative predictive value of NBI for the characterisation of diminutive polyps in the rectosigmoid colon and other regions of the colon

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All characterisations** | | **High confidence characterisations** | |
|  | **Value** | **95% CI** | **Value** | **95% CI** |
| **Rectosigmoid colon diminutive polyps** | | | | |
| Gupta et al.69 | 95.4% | 91.8 to 97.7 | nr | nr |
| Hewett et al. 2012a2 | 98.4% | 95.3% to 99.7% | 99.4% | 96.9% to 100% |
| Ladabaum et al.6 | 87.4% | 82.5 to 92.4 | nr | nr |
| Patel et al.3 | 93.7% | 91.8% to 95.7% | 94.7% | 92.6% to 96.8% |
| Pohl et al.10 | nr | nr | 95.1% | 92.2% to 97.1% a |
| Repici et al.11 | nr | nr | 92% | 88%-96% |
| Wallace et al.12 | 95% | 88.8% to 98.8% a | 96% | 89.3% to 99.2% a |
| **Diminutive polyps located on the right side of the colon** | | | | |
| Kaltenbach et al.5 | nr | nr | 87.1% | 70.2% to 96.4% |
| **Diminutive polyps located proximal to the splenic flexure** | | | | |
| Pohl et al.610 | nr | nr | 43.4% | 33.5% to 53.8% a |
| **Diminutive polyps located on the left side of the colon** | | | | |
| Gupta et al.69 | 93.0 % a | 89.2% to 95.8% a | nr | nr |
| Kaltenbach et al.5 | nr | nr | 93.9% | 83.1% to 98.7% |
| **Diminutive polyps located in the distal colon** | | | | |
| Pohl et al.10 | nr | nr | 92.6% | 89.4% to 95.0% a |
| **Rectal diminutive polyps** | | | | |
| Kaltenbach et al.5 | nr | nr | 93.8% | 79.2% to 99.2% |
| **Diminutive polyps proximal to rectosigmoid colon** | | | | |
| Ladabaum et al.6 | 57.3% | 38.4 to 76.2 | nr | nr |
| Patel et al.3 | 65.6% | 59.2% to 71.9% | 77.1% | 67.9 to 86.2% |
| **Rectosigmoid colon diminutive polyps assessed by endoscopists with prior optical diagnosis experience in colonoscopy** | | | | |
| Pohl et al.10 b |  |  | 96.6% | 92.7% to 98.7% |
| **Rectosigmoid colon diminutive polyps assessed by endoscopists with no prior optical diagnosis experience in colonoscopy** | | | | |
| Pohl et al.10 b |  |  | 93.5% | 88.7% to 96.7% |

a Calculated by reviewer

b There is a discrepancy in this paper between reporting in the text (which states that NPV was for rectosigmoid diminutive adenomas) and in a table which means it is possible that the reported NPVs could relate to polyps in the distal and proximal colon rather than the rectosigmoid.

***Accuracy of NBI***

As well as measures such as sensitivity, specificity and NPV reported above, another global measure, diagnostic accuracy, can be calculated from the 2x2 table data. This is expressed as the proportion of correctly classified polyps (the sum of the true positive and true negative results) among all the ppolyps (true positive + true negative + false positive + false negative). Like NPV diagnostic accuracy is affected by disease prevalence such that at the same sensitivity and specificity diagnostic accuracy increases as disease prevalence decreases.

Accuracy of polyp characterisations in the whole colon was reported by, or could be calculated for, 16 studies (Table 16).3,4,6,7,11-14,67-72,76,78 Accuracy was 90% or more in five studies,67,68,70-72 was between 76% and 89% in ten studies3,4,6,7,11-13,69,76,78 and was only 63.9% in the final study.14

Thirteen studies1,3-14 reported on the accuracy of high confidence polyp characterisations in the whole colon (Table 16). Accuracy was 90% or more in two studies,7,13 was between 81% and 90% in ten studies1,3-6,8-12 and was only 68.5% in the final study.14

Accuracy of polyp characterisation was typically 3-5% higher among high confidence characterisations than all polyp characterisations in the eight studies3,4,6,7,11-14 that reported both values.

Table Accuracy (proportion of correctly classified polyps) with NBI

|  |  |  |
| --- | --- | --- |
|  | **Accuracy of polyp characterisations (95% CI)** | **Accuracy of high confidence polyp characterisations (95% CI)** |
| **Whole colon** | | |
| Aihara et al.67 | 90.1% (84.8 to 95.4) | nr |
| Chandran et al.68 | 91.2% a | nr |
| Gupta et al.69 | 84.8% (82.3 to 87.1) | nr |
| Henry et al.70 | 90.0% (82 to 95) | nr |
| Hewett et al. 2012b1 | nr | 88% |
| Ignjatovic et al.71 | 92% | nr |
| Ikematsu et al.72 | 90.3% | nr |
| Iwatate et al.4 | 79.5% | 85.0% |
| Kaltenbach et al.5 | nr | 87.0% (82.8 to 90.5) |
| Kang et al.78 | 79.4 % (75.5 to 83.6) | nr |
| Ladabaum et al.6 | 78.1% (73.7 to 82.5) | 81.1% (75.8 to 86.3) |
| Lee et al.7 | 87.8% (82.6 to 92.9) | 91.2% a |
| Paggi et al. 20129 | nr | 84.0% |
| Paggi et al. 20158 | nr | 88.2% (83.9 to 92.5) |
| Patel et al.3 | 76.7% (75.2 to 78.3) | 84.8% (82.1 to 87.5) |
| Pohl et al.10 |  | 83.2% |
| Repici et al.11 | 85% | 89% (86 to 92) |
| Rex et al.13 | 88.6% a | 93.0% a |
| Shahid et al.76 | 80% (70 to 87) | nr |
| Sola-Vera et al.14 | 63.9% | 68.5% |
| Wallace et al.12 | 79% | 82% |
| **Whole colon by colonosopist type** | | |
| Iwatate et al.4 |  |  |
| - specialist colonoscopists | nr | 90.7% |
| - generalist colonoscopists | nr | 82.3% |
| **Right colon** | | |
| Kaltenbach et al.5 | nr | 86.4% (80.0 to 91.4) |
| **Proximal to splenic flexure** | | |
| Pohl et al.10 |  | 78.8% |
| **Left colon** | | |
| Gupta et al.69 | 83.5% (80.0 to 86.6) | nr |
| Kaltenbach et al.5 | nr | 90.2% (83.4 to 94.8) |
| **Distal colon** | | |
| Pohl et al.10 |  | 86.2% |
| **Rectosigmoid colon** | | |
| Hewett et al. 2012a2 | 94.5% (91.5 to 97.6) | 99.0% (97.6 to 100) |
| Ladabaum et al.6 | 77.4% (69.1 to 85.3) | nr |
| Patel et al.3 | 80.9% (76.7 to 85.1) | 88.1% (83.2 to 92.9) |
| Repici et al.11 |  | 91% (87 to 95) |
| Pohl et al.10 |  | 87.6% |
| Wallace et al.12 | 84% | 90% |
| **Proximal to rectosigmoid colon** | | |
| Ladabaum et al.6 | 79.3% (74.7 to 83.9) |  |
| Patel et al.3 | 78.8% (75.5 to 82.0 | 84.7% (80.7 to 88.6) |
| **Rectum** | | |
| Kaltenbach et al.5 |  | 80.4% (66.1 to 90.6) |

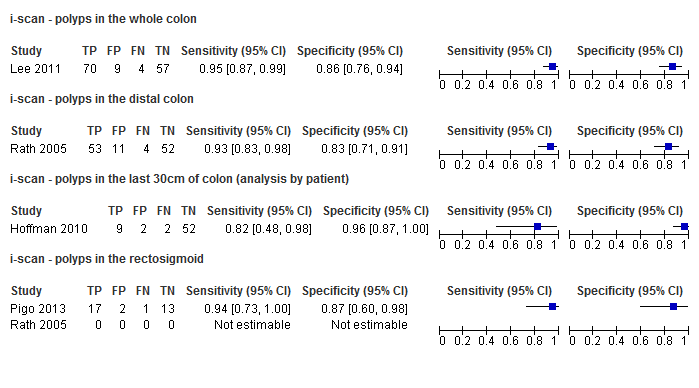
a calculated by reviewer

**i-scan**

***Sensitivity and specificity of i-scan for the characterisation of diminutive colorectal polyps***

Five studies7,79-82 provided data on the characterisation of diminutive polyps as adenomas or hyperplastic polyps using i-scan with the characterisation verified by histopathological assessment of the resected polyps. The way in which data were reported by the studies varied. Two studies, Basford and colleagues79 and Lee and colleagues,7 reported on the characterisation of diminutive polyps within the whole colon. Basford and colleagues only presented data from the polyp characterisations where the endoscopist had high confidence they were correct whereas Lee and colleagues provided data for all characterisations and then separately for characterisations made with either high or low confidence (data for low confidence characterisations is available in Appendix 3). The other three studies presented data on the characterisation of diminutive polyps from within a part of the colon: the distal colon (Rath and colleagues82), the last 30cm of colon (Hoffman and colleagues80) where a per polyp analysis was not presented, only an analysis per patient), and the rectosigmoid colon (Pigo and colleagues81 and Rath and colleagues82 although it was not possible to impute 2x2 table data for this latter study). Rath and colleagues82 also provided data separately for the polyp characterisations they had made with high confidence.

The results for all characterisations (i.e. not separated by confidence level) are shown in Figure 22. The ability of i-scan to correctly identify diminutive polyps as adenomas (ie. the sensitivity of the test) was above 90% in three of the four studies that reported results for all characterisations (Lee and colleagues,7 Pigo and colleagues81 and Rath and colleagues82) whereas sensitivity was only 82% in the per patient analysis reported by Hoffman and colleagues.80 The ability of i-scan to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) was more variable across the studies ranging from 83% (Rath and colleagues82 results for polyps in the distal colon) to 96% (Hoffman and colleagues80).



b

a

a

a 2x2 table data imputed

b Rath 2005 presented summary data for polyps in the rectosigmoid colon but it was not possible for us to impute the 2x2 table data necessary to plot these results within this figure. The reported sensitivity was 90.3% (95% CI 73.1% to 97.5%) and specificity 87.5% (95% CI 74.1% to 94.8%).Temporary reference list for this figure to be processed and removed in production:

Lee et al.7

Rath et al.82

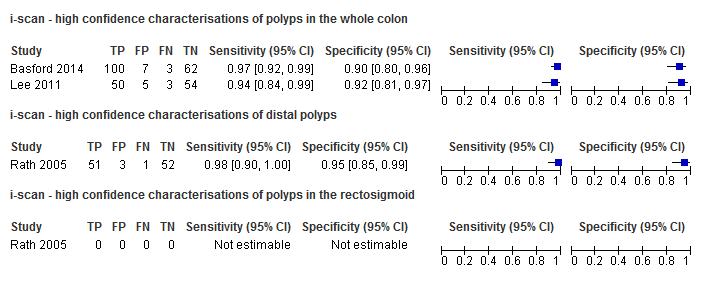
Hoffman et al.80

Pigo et al.81

Rath et al.82

Figure Accuracy of i-scan for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps

Results for studies that reported results from polyp characterisations with i-scan that were designated as high confidence decisions are shown in Figure 23. The ability of high confidence characterisations made with i-scan to correctly identify diminutive polyps as adenomas (ie. the sensitivity of the test) in the three studies that provided data was 0.94 (i.e. 94%) (Lee and colleagues,7), 0.97 (Basford and colleagues79) and in the Rath and colleagues’ study82 0.98 for distal polyps and 0.96 in the analysis limited to polyps in the rectosigmoid colon. For the Lee and colleagues’ study7 the sensitivity achieved from high confidence polyp characterisations was slightly lower than that obtained from all the polyp characterisations 0.94 (95%CI 0.84 to 0.99) versus 0.95 (95% CI 0.87 to 0.99) whereas the reverse was true for the Rath and colleagues’ study82 for both the data set for distal polyps and for rectosigmoid colon polyps (distal polyps: high confidence 0.98, 95% CI 0.90 to 1.00 versus overall 0.93, 95% CI 0.83 to 0.98; rectosigmoid colon: high confidence 0.96, 95% CI 0.80 to 1.0 versus overall 0.90, 95% CI 0.73 to 0.98). The ability of i-scan to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) when the characterisation was made with high confidence was over 0.90 (i.e. 90%) or more in all three studies. Furthermore, the specificity of i-scan arising from high confidence decisions was greater than the specificity observed when all the polyp characterisations were taken into account in the two studies that reported both sets of data (Lee and colleagues7 92% versus 86%; Rath and colleagues82 distal polyps: 95% versus 83%; rectosigmoid colon polyps 95.5% versus 87.5%). The 2005 Rath and colleagues82 study which was conducted in Germany among patients attending for screening or surveillance colonoscopy and which reported on characterisation of distal polyps (polyps in the descending colon, the sigmoid colon, or the rectum) achieved the best sensitivity (98%) which was coupled to the second highest value for specificity (95%). However, in common with the other studies providing data on i-scan, a single endoscopist working in what appears to be a specialist endoscopy centre achieved these results so it is not clear how transferable these results would be to less experienced endoscopists working in less specialist settings.



b

a

a

a 2x2 table data imputed

b Rath 2005 presented summary data for high confidence characterisations of polyps in the rectosigmoid colon but it was not possible for us to impute the 2x2 table data necessary to plot these results within this figure. The reported sensitivity was 96.4% (95% CI 79.8% to 99.8%) and specificity 95.5% (95% CI 83.3% to 99.2%).Temporary reference list for this figure to be processed and removed in production:

Basford et al.79

Lee et al.7

Rath et al.82

Figure Accuracy of i-scan high confidence characterisations of diminutive colorectal polyps as either adenomas or hyperplastic polyps

A bivariate meta-analysis was run (using Stata/IC14 and xtmelogit) to provide a summary estimate for the two studies that reported high confidence characterisations of polyps in the whole colon, which could be used in the economic model. This produced a summary value for sensitivity of 0.96 (95% CI 0.92 to 0.98) and for specificity of 0.91 (95% CI 0.84 to 0.95). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 24.



Summary point

Note that the software used to draw the SROC plot (Review Manager 5.3) did not generate a 95% confidence region or a 95% prediction region for this meta-analysis. It is presumed that this is because of the small number of studies.

Figure SROC plot from the meta-analysis of i-scan for high confidence characterisations of polyps in the whole colon.

***Negative predictive value of i-scan for the characterisation of diminutive colorectal polyps***

As previously stated the negative predictive value is the probability that subjects with a negative screening test (i.e. colorectal polyp is characterised as hyperplastic) truly do not have an adenoma. However, it must be borne in mind when viewing these results that the negative predictive value is influenced by the prevalence of disease (i.e. in this case the prevalence of adenomas in the tested populations). When prevalence is increased the result is a decrease in the negative predictive value.

Two studies7,80 reported NPV for the characterisations of diminutive polyps in the whole colon (made with any level of confidence) although one of these studies, Hoffman and colleagues,80 only reported a per patient analysis. Although the mean NPV was greater 90% the lower limit of the 95% confidence interval fell below 90% in both studies (Table 17). High confidence characterisation of polyps in the whole colon was reported by two studies.7,79 Basford and colleagues79 reported an NPV of 95.4% (95% CI 87.1% to 99.0%) and Lee and colleagues an NPV of 94.7% (95% CI 85.4% to 98.9%).7

Three studies reported on the NPV for the characterisation of diminutive polyps in the distal portion of the colon82 or the rectosigmoid colon,79,81,82 with Rath and colleagues82 also reporting on high confidence characterisations and Basford and colleagues only reporting on high confidence characterisations. In all cases although the point estimate for NPV lay above the 90% threshold the lower limit of the 95% confidence interval fell below this.

Table Negative predictive value of i-scan for the characterisation of diminutive polyps

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All characterisations** | | **High confidence characterisations** | |
|  | Value | 95% CI | Value | 95% CI |
| Whole colon  a |  |  |  |  |
| Basford et al.79 | nr | nr | 95.4% | 87.1% to 99.0% |
| Hoffman et al.80 (per patient analysis) | 96.3 %b | 87.3% to 99.6%b | nr | nr |
| Lee et al.7 | 93.4% | 87.2 to 99.7% | 94.7%b | 85.4% to 98.9%b |
| Distal polyps |  |  |  |  |
| Rath et al.82 | 93.2% | 82.7% to 97.8% | 98.1% | 88.4% to 99.1% |
| Rectosigmoid colon polyps |  |  |  |  |
| Basford et al.79 | nr | nr | 100% | 93.4% to 100.0% |
| Pigo et al.81 | 93% | 81% to 100% | nr | nr |
| Rath et al.82 | 93.3 % | 80.1% to 98.3% | 97.7 % | 86.2% to 99.9% |

a Value calculated by reviewer from imputed values in 2x2 table. b Value calculated by reviewer from 2x2 table data reported in the publication. nr - not reported.

***Accuracy of i-scan***

Diagnostic accuracy (the proportion of correctly classified polyps among all the polyps) was reported either for all diminutive polyp characterisations,80,81 for only high confidence polyp characterisations79 or for both7,82 (Table 18) with three studies providing data for the characterisations of polyps in the whole colon7,79,80 and a single study for polyps in the rectosigmoid colon81 or distal polyps.82 Like NPV diagnostic accuracy is affected by disease prevalence such that at the same sensitivity and specificity diagnostic accuracy increases as disease prevalence decreases.

Accuracy was 90% or more in all the studies7,79-82 and the accuracy of high confidence polyp characterisations was higher that among all polyp characterisations in the two studies that reported both values.7,82

Table Accuracy (proportion of correctly classified polyps) with i-scan

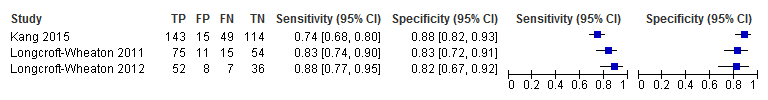
|  |  |  |
| --- | --- | --- |
|  | **Accuracy of polyp characterisations, % (95% CI)** | **Accuracy of high confidence polyp characterisations, % (95% CI)** |
| **Whole colon** | | |
| Basford et al.79 | nr | 94.2% (92.8 to 99.2) |
| Hoffman et al.80 | 94% (per patient analysis) | nr |
| Lee et al.7 | 90.7% (85.9 to 95.5) | 92.9% |
| **Rectosigmoid colon** | | |
| Pigo et al.81 | 91% a | nr |
| **Distal polyps** | | |
| Rath et al.82 | 90.1%a | 96.3% |

a calculated by reviewer

**FICE**

***Sensitivity and specificity of FICE for the characterisation of diminutive colorectal polyps***

Three studies 78,83,84 provided data on the characterisation of diminutive polyps as adenomas or hyperplastic polyps using FICE compared to characterisation verified by histopathological assessment of the resected polyps. In all three studies the characterisations were made on polyps in any part of the colon, and in all three the level of confidence with which the characterisation was made was not stated. The results of the polyp characterisations are shown in Figure 25.



a

a 2x2 table data imputed

Temporary reference list for this figure to be processed and removed in production:

Kang et al.78

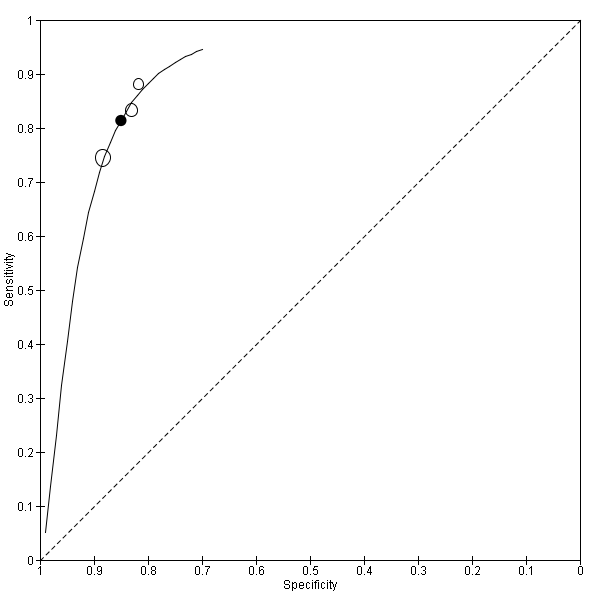
Longcroft-Wheaton et al. 201183

Longcroft-Wheaton et al. 201284

Figure Accuracy of FICE for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps

The ability of FICE to correctly identify diminutive polyps as adenomas (ie. the sensitivity of the test) ranged from 74% to 88% across the studies. The ability of FICE to correctly identify diminutive polyps as hyperplastic polyps (i.e. the specificity of the test) had a narrower range across the studies, from 82% to 88%.

It was possible to run a bivariate meta-analysis (using Stata/IC14 and xtmelogit) with data from the three studies. This produced a summary value for sensitivity of 0.81 (95% CI 0.73 to 0.88) and for specificity of 0.85 (95% CI 0.79 to 0.90). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 26.



Summary point

Note that the software used to draw the SROC plot (Review Manager 5.3) did not generate a 95% confidence region or a 95% prediction region for this meta-analysis. It is presumed that this is because of the small number of studies.

Figure SROC plot from the meta-analysis of FICE for all characterisations of polyps in the whole colon.

***Negative predictive value of FICE for the characterisation of diminutive colorectal polyps***

Table 19 reports the NPVs for the three FICE studies. These ranged from 70% to 84%.

Table Negative predictive value of FICE for the characterisation of diminutive colorectal polyps

|  |  |  |
| --- | --- | --- |
| **Study** | **Value** | **95% CI** |
| Kang et al.78 | 70% | 63% to 77% |
| Longcroft-Wheaton et al. 201183 | 78% | 70% to 84% |
| Longcroft-Wheaton et al. 201284 | 84%a | 69% to 93%a |

a Value calculated by the reviewer

***Accuracy of FICE***

The three studies that reported on the use of FICE provided diagnostic accuracy (the proportion of correctly classified polyps among all the polyps) for all diminutive polyp characterisations in the whole colon (Table 20).78,83,84 The reported diagnostic accuracy values ranged from 80% to 85%.

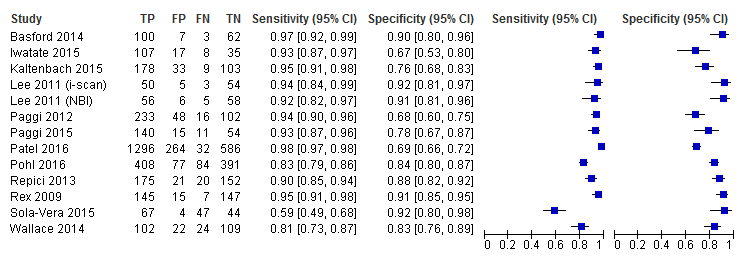
Table Accuracy (proportion of correctly classified polyps) with FICE

|  |  |  |
| --- | --- | --- |
|  | **Accuracy of polyp characterisations, % (95% CI)** | **Accuracy of high confidence polyp characterisations, % (95% CI)** |
| **Whole colon** | | |
| Kang et al.78 | 80.1% (75.8 to 84.6) | nr |
| Longcroft-Wheaton et al. 201183 | 83% (77% to 88%) | nr |
| Longcroft-Wheaton et al. 201284 | 85% (76 to 91) | nr |

**Post-hoc pooled analysis of all virtual chromoendoscopy technologies**

The appropriateness of pooling evidence from different virtual chromoendoscopy technologies together is uncertain. The technologies certainly all aim to enhance surface vessel patterns but the technologies use different methods to achieve this. We have therefore assumed that there is a ‘class effect’and that they can be meaningfully pooled.

A pooled analysis of the studies included in this assessment for which 2x2 data were available was undertaken in order to inform a scenario analysis using the economic model (section ‎5.5.2). Data for high confidence assessments of polyps in the whole colon were available from 11 NBI studies and two i-scan studies (note that Lee and colleagues7 contribute data on NBI and i-scan) (Figure 27). No FICE data were available to include in this analysis because the FICE studies did not report high confidence polyp characterisation separately.



Temporary reference list for this figure to be processed and removed in production:

Basford et al.79

Iwatate et al.4

Kaltenbach et al.5

Lee et al.7

Lee et al.7

Paggi et al. 20129

Paggi et al. 20158

Patel et al.3

Pohl et al.10

Repici et al.11

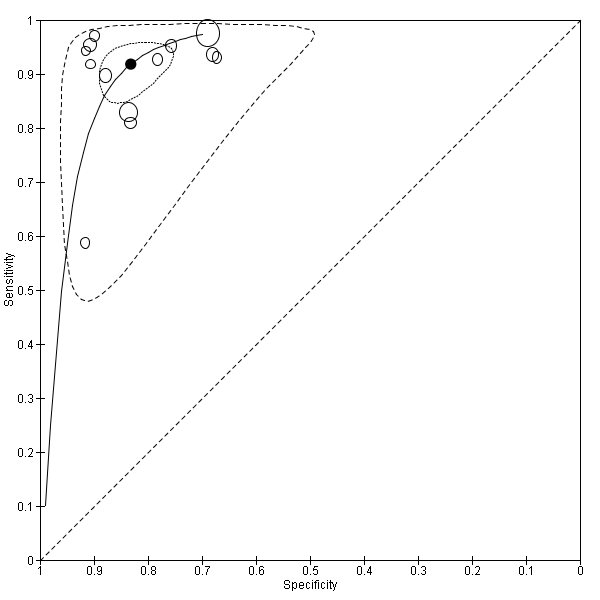
Rex et al.13

Sola-Vera et al.14

Wallace et al.12

Figure Accuracy of virtual chromoendoscopy high confidence decisions for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps in the whole colon

A bivariate meta-analysis (using Stata/IC14 and metandi57) was carried out which produced a pooled summary estimate for sensitivity of 0.92 (95% CI 0.87 to 0.95) and for specificity of 0.83 (95% CI 0.78 to 0.87). The parameter estimates for the bivariate model were entered into RevMan to produce the SROC plot shown below in Figure 28. The virtual chromoendoscopy pooled estimates for sensitivity and specificity do not differ greatly from the NBI pooled estimates (Figure 9) which is unsurprising given that the bulk of the evidence comes from studies of NBI.



…..… 95% confidence region

95**%** prediction region

Summary point

Figure SROC plot showing the summary point on the summary curve from the meta-analysis of virtual chromoendoscopy high confidence decisions for characterising diminutive colorectal polyps in the whole colon

A pooled analysis of the virtual chromoendscopy studies for high confidence assessments of polyps in the rectosigmoid colon, equivalent to that above for the whole colon, has in essence already been presented earlier in this assessment. This is because the only data available for this analysis come from NBI studies and thus the results presented in Figure 15 and Figure 16 represent all the available data on high confidence assessments of polyps in the rectosigmoid colon, there are no equivalent data for i-scan or FICE.

* + 1. Assessment of test impact on recommended surveillance intervals

**NBI**

Thirteen studies3,5,6,9-14,68,69,71,77 reported results on the impact that the use of NBI would have on recommended surveillance intervals (in comparison to surveillance intervals calculated following histopathology of all polyps) (Table 21). The agreement between the surveillance interval allocated using an NBI based strategy and using the results of histopathology for all polyps ranged from 84%12,77 to 99 %.11 Eleven of the 13 studies reporting on this outcome achieved a level of agreement that was above 90%3,5,6,10-14,68,69,71 although for three of these studies6,12,69 an agreement of over 90% was only achieved by one of the tested strategies (in two studies using a modified recommendation of colonoscopy in 10 years for patients with 1-2 small adenomas instead of 5 years,6,69 and in one study limiting the analysis to where there was a high confidence predictions for polyps ≤5mm12). Where there were discrepancies between the surveillance interval assigned using the NBI based strategy and the histopathology only strategy some studies reported whether the NBI strategy led to longer or shorter surveillance intervals being assigned. In the majority of studies where a discrepancy in the surveillance interval was reported, the NBI containing strategy more often led to shorter surveillance intervals being set (i.e. patients recalled for a colonoscopy earlier than would have been the case with the histopathology based surveillance interval) than longer surveillance intervals. There were however some exceptions, particularly the study by Repici and colleagues11 where, if there was a difference between the surveillance intervals assigned, the NBI containing strategy was more likely to lead to the assignment of a longer interval (i.e. patients not recalled for repeat colonoscopy as early as they would have been with the histopathology based surveillance interval) than a shorter one.

Nine studies clearly calculated the concordance of surveillance intervals between virtual chromoendoscopy and histopathology in line with the PIVI requirements.5,6,8,10-13,68,77 The criterion of the PIVI statement, that agreement should be ≥90%, was met by all but one study,77 with one further study meeting the PIVI criterion in one of the two tested strategies.6 Where the agreement was ≥90% the lower limit of the 95% confidence interval (where reported) fell below 90% in two instances.3,11

Table Surveillance interval prediction

| **Study** | **Guideline used for determining surveillance interval (as cited by the study)** | **Surveillance interval correctly allocated [95% CI] (n/N)** | **Shorter or longer intervals set with NBI, n (% of total allocations)** |
| --- | --- | --- | --- |
| Chandran et al.68 | NHMRC, Australia 2011100 | 98% (92/94) | 2 (2%) shorter |
| Gupta et al.69 | Multi-Society Task Force 2008101: A] colonoscopy in 3 years for patients with ≥3 adenomas or ≥1 advanced adenomas, 5 years for patients with 1-2 small adenomas without advanced histology,& 10 years for patients with 0 adenomas | 86.1% [95% CI 82.4 to 89.3] |  |
| Multi-Society Task Force 2008101: B] colonoscopy in 3 years for patients with ≥3 adenomas or with ≥1 advanced adenomas & 10 years for patients with 1-2 small adenomas or 0 adenomas. | 94.1% [95% CI 91.4 to 96.2] |  |
| Ignjatovic et al.71 | BSG guidelines 200241  (& based on patients with no polyps >10mm) | 98% (80/82) | 2 (2%) shorter |
| Kaltenbach et al.5 | US Multi-Society Task Force 2012102 |  |  |
| - Overall | 92.2% (259/281) |  |
| - High confidence NBI diagnosis+ histopathology for all other polyps | 95.2% (200/210)a | 7 (3.3%) shorter  3 (1.4%) longer |
| Ladabaum et al.6 | Multi-Society Task Force 2008101 |  |  |
| - All study colonoscopies (n=1646) | 88.4% [95% CI 86.8 to 89.9] |  |
| - All study colonoscopies with ≥1 diminutive polyp characterised with high confidence (n=1065) | 79.9% [95% CI 77.4 to 82.3]a | 136 (13%) shorter  78 (7%) longer |
| Using modified recommendations 201269 (10 year for 1-2 small adenomas) |  |  |
| - All study colonoscopies (n=1646) | 98.4% [95% CI 97.6 to 98.9] |  |
| - All study colonoscopies with ≥1 diminutive polyp characterised with high confidence (n=1065) | 96.8% [95% CI 95.6 to 97.8]a | 24 (2%) shorter  10 (1%) longer |
| Paggi et al. 20128 | US Multi-Society Task Force on Colorectal Cancer (USMSTF) 2006.103 | 85.3% (168/197) | 22 (11%) shorter  7 (4%) longer |
| Patel et al.3 | US Multi-Society Task Force 2012102 | 91.2% [95% CI 89.67 to 92.65] (1279/1403)a | 82 (5.8%) shorter  39 (2.8%) longer |
| Pohl et al.10 b | US multi-society taskforce guidelines102,104 |  |  |
| - All study colonoscopies | 96% |  |
| - All study colonoscopies with ≥1 diminutive polyp (n=566) | 93%a | 24 (4%) shorter  15 (3%) longer |
| Repici et al.11 | European Guidelines 2010105: ≥1 polyp ≤5mm characterised with high confidence | 99% [95% CI, 97%-100%]a | 3 (1%) longer |
| Multi-Society Task Force 2008101 |  |  |
| - ≥ 1 polyp ≤5mm characterised with high confidence & 5- year interval for non-advanced adenomas ≤ 2mm | 92% [95% CI 88%-96%]a | 5 (2%) shorter  12 (4%) longer |
| - ≥ 1 polyp ≤5mm characterised with high confidence & 10- year interval for non-advanced adenomas ≤ 2mm | 99% [95% CI, 97%-100%]a | 3 (1%) longer |
| Rex et al.13 | US Multi-Society Task Force on Colorectal Cancer (USMSTF) 2006.103 |  |  |
| - Colonscopy in 5 years if 1 or 2 tubular adenomas <1 cm in size. | 94% (128/136)a | 4 (3%) shorter  4 (3%) longer |
| - Colonscopy in 10 years if 1 or 2 tubular adenomas <1 cm in size. | 98.5% (134/136)a | 2 (1%) shorter  1 (0.7%) longer |
| Sola-Vera et al.14 | European Guideline 2012106 | 97.8% (46/47) | nr |
| ESGE Guideline107 | 97.8% (46/47) | nr |
| Vu et al.77 | Multi-Society Task Force 2008,101 high confidence predictions | 84.1%a | nr |
| Wallace et al.12 | Based only on number and size of adenomas108 |  |  |
| - All predictions | 84% [95% CIs 79% - 88%] (221/264) | 27 (10%) shorter  16 (6%) longer |
| - High confidence predictions for polyps ≤5mm | 95% [95% CIs 91% - 97%] (250/264)a | 5 (2%) shorter  9 (3%) longer |

NHMRC - National Health and Medical Research Council

a Results from analyses of surveillance interval agreement in accordance with PIVI requirements

b Pohl and colleagues also reported surveillance interval results by colonoscopists experience and there was no statistically significant difference between the two (Appendix 3).

**i-scan**

Two studies79,82 examined the effect that use of i-scan had on recommended surveillance intervals in comparison to those that were allocated based on histopathological assessment of all polyps (Table 22). Both studies79,82 used *in vivo* diagnosis of diminutive polyps to guide surveillance interval decisions in accordance with the PIVI requirements. Both studies79,82 also calculated agreement in surveillance intervals between i-scan and histopathology when using two different guidelines for determining the surveillance interval. Across these two studies, a surveillance interval agreement of over 90% was achieved regardless of the guideline used, with agreement ranging from 93.2%82 to 97.2%.79 In the study by Basford and colleagues,79 identical results (an agreement of 97.2%) were achieved when using both the guidelines assessed. Both studies reported whether using i-scan resulted in a longer or shorter surveillance interval being allocated than that allocated by histopathology. In the Basford and colleagues’ study,79 two patients were set a shorter interval with i-scan and one patient a longer interval. In the Rath and colleagues’ study,82 i-scan tended to results in longer intervals being allocated than with histopathology, except in one case.

Table Surveillance interval prediction using i-scan

| **Study** | **Guideline used for determining surveillance interval (as cited by the study)** | **Surveillance interval correctly allocated % [95% CI] (n/N)** | **Longer or shorter intervals set with i-scan, n (% of total allocations)** |
| --- | --- | --- | --- |
| i-scan surveillance intervals based on high confidence assessment of all diminutive polyps combined with histology of polyps >5mm | | | |
| Basford et al.79 | American Society of Gastroenterology (ASGE)102 and British Society of Gastroenterology (BSG) guidelines41 | 97.2% [not reported] (80/83) | 2 (2.4%) shorter  1 (1.2%) longer |
| i-scan surveillance intervals based on high confidence assessment of all distal polyps | | | |
| Rath et al.82 a | European guidelines106 | 94.5% [not reported] (69/73) | 4 (5.5%) longer |
| US guidelines102 | 93.2% [not reported] (68/73) | 1 (1.4%) shorter  4 (5.5%) longer |

a The surveillance intervals determined in this study were based on the assessment of polyps in the distal colon only. Surveillance intervals for polyps in the rectosigmoid were also reported, but are not presented here.

**FICE**

Two studies83,84 reported results on the impact that the use of FICE would have on recommended surveillance intervals (in comparison to surveillance intervals calculated following histopathology of all polyps) although neither assessed this in accordance with the PIVI criteria. This analysis, in both of these studies, included polyps <10mm (i.e. neither was restricted to diminutive polyps). The agreement between the surveillance interval allocated using a FICE based strategy and using the results of histopathology was 100% in one study83 and 97% in the other study84 regardless of whether the BSG or ASGE guidelines were used to determine the surveillance intervals. In the single study where there was a discrepancy for two participants between the surveillance interval assigned using the FICE based strategy and the histopathology strategy it is not known whether the FICE based strategy led to a longer or a shorter surveillance interval being set (Table 23).

Table Surveillance interval prediction using FICE

| **Study** | **Guideline used for determining surveillance interval (as cited by the study)** | **Surveillance interval correctly allocated % [95% CI] (n/N)** | **Longer or shorter intervals set with FICE, n (% of total allocations)** |
| --- | --- | --- | --- |
| Longcroft-Wheaton et al. 201283 a | British Society of Gastroenterology (BSG)41 | 100% (38/38) | n/a |
| ASGE109 | 100% (38/38) | n/a |
| Longcroft-Wheaton et al. 201184 a | British Society of Gastroenterology (BSG)41 | 97% [89% to 100%] (67/69) | Not reported |
| ASGE109 | 97% [89% to 100%] (67/69) | Not reported |

a Patients with lesions >10mm would have required histology to set the surveillance interval and so were excluded from these analyses.

* + 1. Assessment of other outcomes

In addition to the outcomes reported above on test accuracy and the impact on recommended surveillance intervals the review also aimed to report data on the interpretability of the tests; inter-observer agreement; intra-observer agreement; test acceptability (to patients and/or clinicians); adverse events; the number of polyps designated to be left in place; the number of polyps designated to be resected and discarded; the number of polyps designated for resection and histopathological examination; the length of time to perform the colonoscopy; the number of outpatient appointments; health-related quality of life; incidence of colorectal cancer and mortality.

**NBI**

None of the studies reported on the interpretability of the test; test acceptability (to patients and/or clinicians), number of outpatients appointments, health-related quality of life, incidence of colorectal cancer, or mortality.

One study, Lee and colleagues7 reported on inter-observer agreement although this was the agreement between the characterisation obtained during real-time assessment and that obtained by an independent reader who reviewed all recorded endoscopic images whilst blind to the real-time assessement and the histopathology results. The inter-observer agreement was 86.5% with a k value (95% CI) of 0.730 (0.623 to 0.837) which represents ‘substantial’ agreement. One other study, Rogart and colleagues75 reported inter-observer agreement for 20 test images but as this did not include any real-time assessment these data were not extracted. Lee and colleagues7 were also the only researchers to report on intra-observer agreement. This was the agreement between the between the characterisation obtained during real-time assessment and that obtained by the same endoscopist who reviewed all recorded endoscopic images 1-3 months after the colonoscopy. The intra-observer agreement was 89.7% with a k value (95% CI) of 0.795 (0.699 to 0.890) again representing ‘substantial’ agreement.

Adverse events were not reported by most studies.1-4,6,8-14,67-72,75,77,78 Of the three studies that did make mention of potential adverse events5,7,76 the reports all indicated that no events had occurred. Kaltenbach and colleagues5 reported no postpolypectomy bleeding, coagulation syndrome, perforation, or optical misdiagnosis of advanced histology, Lee and colleagues7 stated that participants did not experience any procedure-related complications and Shahid and colleagues76 stated that none of the patients experienced any endoscopic complications.

Ignatovic and colleagues71reported on the number of diminutive polyps that would have been left in place if the management strategy was to leave diminutive hyperplastic polps in situ in the recto-sigmoid colon. The endoscopists in this study made a high confidence optical diagnosis for 323 polyps (<10mm in this study) and of these, 33 would have been left in situ. All 33 were correctly predicted to be hyperplastic polyps and all were located in the sigmoid colon or the rectum. One other study, Repici and colleagues,11 made a statement indicating that in their study, a discard type strategy would have reduced the need for polypectomy by 48%.

Two studies reported on the number of polyps that would have been resected and discarded if a resect and discard type of management strategy had been in place. Gupta and colleagues69 reported a hypothetical strategy in which if all the 884 diminutive polyps in their study (where the total number of polyps of any size was 1254) were resected and discarded this would represent a 70.5% reduction in histopathology. Using this strategy 13 adenomas with advanced histologic features would have been discarded. However, it must be noted that this study did not record whether characterisations were made with high or low confidence and did not report how many diminutive polyps were in the rectosigmoid colon. Ignatovic and colleagues71 reported a high confidence optical diagnosis was made for 323 polyps (<10mm in this study) and of these 290 would have been resected and discarded. The Ignatovic and colleagues’ study71 was the only NBI study to ask endoscopists to identify polyps that they would have sent electively to histopathology even if a policy of optical diagnosis had been in place. These were polyps where the optical diagnosis was made with low confidence or where no optical diagnosis could be made. For the sub-group of diminutive polyps in this study 8% (22 of 293 polyps) would have been sent for elective histopathology.

The length of time taken to perform the withdrawal phase of the colonoscopy was reported by three studies. Kaltenbach and colleagues5 reported a mean withdrawal time of 10.3 minutes (SD 5.7, range 3.3 to 58 minutes). A procedure time of 12 seconds is reported but a definition of procedure time is not provided in the study publication so it is not clear what this comprises. In the Kang and colleagues78 study the mean withdrawal time in the NBI group was 13.5 minutes (SD 7.3) whilst in the Wallace and colleagues’ study12 it was 16.1 minutes (SD 7.3). A fourth study, Shahid and colleagues,76 reported that the average withdrawal time at their centre was typically eight to 10 minutes but it was not reported specifically for their study. However they did report that NBI inspection time was typically less than a minute.

**i-scan**

None of the studies reported on the interpretability of the test, test acceptability (to patients and/or clinicians), 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, number of outpatients appointments, health-related quality of life, incidence of colorectal cancer, or mortality.

One study, Lee and colleagues7 reported on inter-observer agreement although this was the agreement between the characterisation obtained during real-time assessment and that obtained by an independent reader who reviewed all recorded endoscopic images whilst blind to the real-time assessement and the histopathology results. The inter-observer agreement was 87.9% with a k value (95% CI) of 0.751 (0.640 to 0.861) which represents ‘substantial’ agreement. One other study, Pigo and colleagues81 reported inter-observer agreement but this was based on endoscopists’ assessments of still images so because this did not include any real-time assessment these data were not extracted. Two studies, Lee and colleagues7 and Rath and colleagues82 reported on intra-observer agreement. In the Lee and colleagues’ study7 this was the agreement between the characterisation obtained during real-time assessment and that obtained by the same endoscopist who reviewed all recorded endoscopic images 1-3 months after the colonoscopy. The intra-observer agreement was 86.4% with a k value (95% CI) of 0.729 (0.616 to 0.841) again representing ‘substantial’ agreement. In the Rath and colleagues’ study82 it is not clear how intra-observer agreement was assessed because no details are reported in the paper. The authors state that agreement was achieved in 113 out of 121 polyps (93.4 %) with a κ coefficient of agreement of 0.867 [95 % CI: 0.799–0.967] which indicated almost perfect agreement. In the Pigo and colleagues’ study81 intra-observer agreement was assessed based on the endoscopists’ assessment of still images rather than real-time assessment and furthermore the intra-observer agreement for the evaluation of diminutive polyps was not reported so these data were not extracted.

As already stated in the NBI section, Lee and colleagues7 stated that participants did not experience any procedure-related complications. The other four i-scan studies79-82 made no reports of adverse events.

The length of time taken to perform the withdrawal phase of the colonoscopy was not reported in any of the studies. Basford and colleagues79 however, commented that the in vivo assessment was performed in the time between finding a polyp and preparing for polypectomy and so did not cause a significant delay. Hoffman and colleagues,80 who examined only the last 30cm of colon reported that with surface enhancement with i-scan the total examination time was 5 minutes.

**FICE**

None of the studies reported on the interpretability of test, inter-observer agreement, intra-observer agreement, test acceptability (to patients and/or clinicians), adverse events, 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, length of time to perform the colonoscopy, number of outpatient appointments, health-related quality of life, incidence of colorectal cancer or mortality.

**Head-to-head comparisons**

Head-to-head comparisons of NBI, i-scan and FICE were not within the scope of this assessment, nevertheless two studies met the inclusion criteria for the systematic review which did compare two technologies against each other. When NBI was compared to i-scan in a prospective cohort study of the real-time histological prediction of diminutive colonic polyps, Lee and colleagues7 found no statistically significant differences between the two technologies (NBI vs i-scan: sensitivity, 88.8% vs 94.6%; specificity, 86.8% vs 86.4%; accuracy, 87.8% vs 90.7%, respectively; P > 0.05). In the RCT that compared NBI to FICE, Kang and colleagues78 found that for polyps <5mm in size there was no statistically significant difference (P>0.05) in accuracy (74.9% vs 80.1%, respectively) or sensitivity (81.9% vs 74.5 %) but there was a statistically significant difference in specificity (75.7% vs. 88.4 %, P = 0.006). The authors concluded that better results should be achieved for both technologies before either are used for real-time optical biopsy of colorectal polyps in colorectal screening of the general population.78 It is worth noting that in the study by Lee and colleagues7 a single endoscopist with experienced of both NBI and i-scan undertook the study colonoscopies whereas the four endoscopists in the Kang and colleagues’ study78 had no prior experience of either NBI or FICE.

* + 1. Summary of diagnostic test performance evidence
* Thirty studies met the inclusion criteria for the systematic review of test accuracy. These assessed NBI (24 studies), i-scan (5 studies) and FICE (3 studies). Two of the included studies assessed two of the included interventions (NBI and i-scan; NBI and FICE). The way studies reported test accuracy outcomes (in terms of the region of the colon and the level of confidence assigned to the polyp characterisation) varied.
* Most studies enrolled participants from more than one of the populations eligible for inclusion in this review (receiving colonoscopy for screening, surveillance, or symptoms) but these studies did not report results separately for each participant type.
* The included studies were judged as likely to be at a low risk of bias.

**NBI**

* 23 studies reported either sensitivity (1 study) or both sensitivity and specificity (22 studies).
* In the whole colon, characterisations of diminutive polyps made with any level of confidence had a sensitivity ranging from 0.55 to 0.97 (17 studies) and a specificity ranging from 0.62 to 0.95 (16 studies). A bivariate meta-analysis (15 studies) produced a summary sensitivity value of 0.87 (95% CI 0.82 to 0.91) and specificity of 0.81 (95% CI 0.75 to 0.85). For characterisations in the whole colon made with high confidence summary sensitivity and specificity (11 studies) was slightly higher: sensitivity 0.91 (95% CI 0.85 to 0.95) and for specificity of 0.82 (95% CI 0.76 to 0.87) and limiting this analysis to studies where the endoscopists were experienced in the use of NBI (4 studies) did not greatly alter these results [sensitivity 0.92 (95% CI 0.89 to 0.94); specificity 0.82 (95% CI 0.72 to 0.89)].
* In the rectosigmoid colon, characterisations of diminutive polyps made with any level of confidence (four studies) had a sensitivity ranging from 0.84 to 0.90 and a specificity ranging from 0.76 to 0.95. A bivariate meta-analysis (3 studies) produced a summary estimate for sensitivity of 0.85 (95% CI 0.75 to 0.91) and for specificity of 0.87 (95% CI 0.74 to 0.94). For characterisations in the rectosigmoid colon made with high confidence (5 studies) sensitivity ranged from 0.83 to 0.96 and specificity from 88% to 99%. A bivariate meta-analysis (4 studies) produced a summary estimate for sensitivity of 0.87 (95% CI 0.80, 0.92) and for specificity of 0.95 (95% CI 0.87, 0.98). Limiting the analysis of high confidence characterisations in the rectosigmoid colon to the two studies where the endoscopists were experienced in the use of NBI increased the summary values for sensitivity and specificity [sensitivity: 0.90 (95% CI 0.71 to 0.97); specificity 0.98 (95% CI 0.91 to 1.00)].
* Some studies that reported sensitivity and specificity were not included in meta-analysis because it was not possible to impute the required 2x2 table data. In two of three instances where this occurred, the sensitivity and specificity reported by the absent study lay within the 95% CI of the summary estimates of the meta-analysis. In one case (the meta-analysis of high confidence polyp characterisations in the whole colon) the missing study, Ladabaum and colleagues,6 reported a sensitivity that lay within the 95% CI of the summary estimate but a specificity that lay outside the 95% CI of the summary estimate.
* The NPV of NBI for the characterisation of diminutive polyps in the whole colon (made with any level of confidence) ranges from 43% to 96% (16 studies). Five studies reported NPV values of 90% or more but the lower limit of the 95% confidence interval fell below 90% in every study except one. When limited to high confidence characterisations NPV ranged from 48% to 98% (13 studies) with five studies reporting NPV values of 90% or more. However, the lower limit of the 95% CI remained above 90% in only two studies.
* The NPV of NBI for the characterisation of diminutive polyps in the rectosigmoid colon (made with any level of confidence) ranged from 87% to 98% and was over 90% in four out of the five studies that reported this outcome (but the lower limit of the 95% CI remained above 90% in only two studies). When limited to high confidence characterisations in the rectosigmoid colon (five studies), NPV ranged from 92% to 99% but the lower limit of the 95% CI fell below 90% in 2 studies.
* Accuracy (the proportion of correctly classified polyps) of polyp characterisations in the whole colon was 90% or more in five studies and lay between 76% and 89% in 10 studies (16 studies reported this outcome). High confidence characterisations typically increased accuracy by 3-5% in studies reporting both overall and high confidence data (8 studies).
* Agreement between the surveillance interval allocated using an NBI based strategy and using the results of histopathology was above 90% in eleven of the 13 studies that reported this outcome. When there was a discrepancy in surveillance intervals, the NBI containing strategy more often led to an earlier recall for colonoscopy than would have occurred with the histopathology based surveillance interval.
* No outcome data were reported (Interpretability of the test; test acceptability, number of outpatients appointments, health-related quality of life, incidence of colorectal cancer, or mortality) or sparse outcome data (inter-observer agreement, adverse events, polyps designated as ‘left in place’, polyps designated ‘resect and discard’, time taken to perform colonoscopy) were reported for other outcomes of interest to this review

**i-scan**

* Five studies provided sensitivity and specificity outcomes for the characterisation of diminutive polyps as adenomas or hyperplastic polyps using i-scan. Often only a single study provided data for a particular combination of the region of the colon and the level of confidence assigned to the polyp characterisation.
* In the whole colon or in regions of the colon characterisations of diminutive polyps made with any level of confidence ranged in sensitivity from 0.82 to 0.95 and in specificity from 0.83 to 0.96. It was not possible to meta-analyse any of these results. For high confidence characterisations in the whole colon or in regions of the colon sensitivity ranged from 94% to 98% and specificity from 90% to 95%. The only meta-analysis possible, which was conducted to inform the economic model, was for high confidence characterisations of diminutive polyps in the whole colon. The summary value for sensitivity was 0.96 (95% CI 0.92 to 0.98) and for specificity was 0.91 (95% CI 0.84 to 0.95).
* NPV values were above 90% (all 5 studies) however the lower limit 95% confidence interval was above 90% in only one study.
* Accuracy was 90% or more (all 5 studies) and higher for high confidence polyp characterisations in the two studies that also reported accuracy for all polyp characterisations.
* Surveillance interval agreement (2 studies) determined by i-scan and histopathology was over 90%. Where surveillance intervals differed, longer intervals were more likely to be set with i-scan than histopathology.
* No outcome data were reported (Interpretability of the test; test acceptability, polyps designated as ‘left in place’, polyps designated ‘resect and discard’, number of outpatients appointments, health-related quality of life, incidence of colorectal cancer, or mortality) or sparse outcome data (inter-observer agreement, adverse events, time taken to perform colonoscopy) were reported for other outcomes of interest to this review

**FICE**

* Three studies provided sensitivity and specificity with all reporting on characterisations of diminutive polyps made with any level of confidence in the whole colon. Reported values for sensitivity range from 74% to 88% and for specificity from 82% to 88%.
* None of the studies provided evidence on the high confidence characterisation of diminutive polyps or restricted their analysis to a part of the colon e.g. the rectosigmoid colon.
* It was possible to run a bivariate meta-analysis that produced a summary estimate for sensitivity of 0.81 (95% CI 0.73 to 0.88) and for specificity of 0.85 (95% CI 0.79 to 0.90).
* The NPV of FICE (3 studies) ranged from 70% to 84%.
* The accuracy of FICE (3 studies) ranged from 80% to 85%
* Surveillance interval agreement between FICE and histopathology was 100% (1 study) or 97% (1 study). When there was disagreement it was not reported whether the FICE based strategy led to a longer or a shorter surveillance interval being set.
* None of the other outcomes of interest to this review were reported.

**Pooled analysis of virtual chromoendoscopy technologies**

* A pooled analysis of high confidence decisions characterising diminutive polyps in the whole colon (11 NBI, 2 i-scan studies) was undertaken to inform a scenario analysis using the economic model. This produced a pooled summary estimate for sensitivity of 0.92 (95% CI 0.87 to 0.95) and for specificity of 0.83 (95% CI 0.78 to 0.87).

**Head-to-head comparisons**

* Head-to-head comparisons of the technologies were not within the scope for this assessment, but two included studies compare two technologies against each other. For the real-time histological prediction of diminutive colonic polyps no statistically significant differences were found when a single endoscopist with experience of NBI and i-scan compared these technologies in a prospective cohort study. An RCT conducted by endoscopists without experience of either NBI to FICE found no statistically significant difference in accuracy or sensitivity but a statistically significant difference in specificity.

Table 24 provides a summary of the pooled sensitivity and specificity values from our bivariate meta-analysis, where available.

Table Summary of bivariate meta-analysis results

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Type of characterisation** | **Diminutive polyp location** | **NBI** | | **i-scan** | | **FICE** | |
| Sensitivity  (95% CI) | Specificity  (95% CI) | Sensitivity  (95% CI) | Specificity  (95% CI) | Sensitivity  (95% CI) | Specificity  (95% CI) |
| All characterisations a | whole colon | 0.88  (0.83 to 0.92)  16 studies | 0.81  (0.75 to 0.85)  16 studies | *0.95*  *(0.87 to 0.99)*  *Single study* | *0.86*  *(0.76 to 0.94)*  *Single study* | 0.81  (0.73 to 0.88)  3 studies | 0.85  (0.79 to 0.90)  3 studies |
| High confidence characterisations | whole colon | 0.91  (0.85 to 0.95)  11 studies | 0.82  (0.76 to 0.87)  11 studies | 0.96  (0.92 to 0.98)b  2 studies | 0.91  (0.84 to 0.95)b  2 studies | No evidence | No evidence |
| High confidence characterisations by endoscopists with prior experience of the technology c | whole colon | 0.92  (0.89 to 0.94)  4 studies | 0.82  (0.72 to 0.89)  4 studies | 0.96  (0.92 to 0.98)b  2 studies | 0.91  (0.84 to 0.95)b  2 studies | No evidence | No evidence |
|
| All characterisations a | rectosigmoid colon | 0.85  (0.75 to 0.91)  3 studies | 0.87  (0.74 to 0.94)  3 studies | Meta-analysis not possible  2 studies | Meta-analysis not possible  2 studies | No evidence | No evidence |
| High confidence characterisations | rectosigmoid colon | 0.87  (0.80 to 0.92)  4 studies | 0.95  (0.87 to 0.98)  4 studies | *0.96*  *(0.80 to 1.00)*  *Single study* | *0.96*  *(0.83 to 0.99)*  *Single study* | No evidence | No evidence |
| High confidence characterisations by endoscopists with prior experience of the technology c | rectosigmoid colon | 0.90  (0.71 to 0.97)  2 studies | 0.98  (0.91 to 1.00)  2 studies | No evidence | No evidence | No evidence | No evidence |
|  |  | **Pooled analysis of virtual chromoendoscopy technologies** | | | | | |
|  |  | Sensitivity (95% CI) | | | Specificity (95% CI) | | |
| High confidence characterisations c | whole colon | 0.92 (0.87 to 0.95)  11 NBI studies, 2 i-scan studies | | | 0.83 (0.78 to 0.87)  11 NBI studies, 2 i-scan studies | | |

aAll characterisations means not separated by endoscopist confidence level.

b The ‘High confidence characterisations’ result and the ‘High confidence characterisations by endoscopists with prior experience of the technology’ result are identical because the two studies contributing data to the high confidence meta-analysis were both undertaken by endoscopists with prior experience in using NBI.

c Post-hoc analysis

* 1. Ongoing studies

We identified 19 potentially relevant ongoing studies on the use of NBI, i-scan or FICE to characterise diminutive colorectal polyps. Two were identified from searches of clinical trials databases (see Section ‎3.1 for details of these searches) and 17 were identified from conference abstracts found by the clinical effectiveness searches. Until further details are available it is not clear whether all would meet the eligibility criteria for this review but they have the potential to do so. These studies are listed in Appendix 5.

1. ECONOMIC ANALYSIS

This section consists of a systematic review of published cost-effectiveness analyses of virtual chromoendoscopy compared to histopathology and a de novo economic evaluation.

* 1. Systematic review of existing cost-effectiveness evidence

This section describes the systematic review of published cost-effectiveness analyses of virtual chromoendoscopy. The aim of the systematic review was to inform the development of the independent economic evaluation. The same search strategy that was used to identify diagnostic test studies was used to identify cost-effectiveness studies, as described in Section 3. Once the results of this search had been downloaded into our Endnote (X7.0.2, Thomson Reuters) bibliographic database we searched for a subset of relevant cost-effectiveness studies using the keyword ‘cost’ in any field (NB. The search strategy for our systematic review of diagnostic accuracy did use a study design filter, therefore it would not have excluded any relevant health economic studies). Titles and abstracts were then screened by two health economists for relevance according to the inclusion criteria. The inclusion criteria were for a full economic evaluation (cost-effectiveness, cost-utility, cost benefit or cost consequence analysis) that compared virtual chromoendoscopy with conventional (white light) colonoscopy for adults undergoing a colonoscopy for detection of colorectal polyps, that included long-term outcomes (such as life years, incidence of colorectal cancer or QALYs). Full texts of references deemed relevant were then retrieved for further screening. The full texts of retrieved references were screened to identify those that met the inclusion criteria. Data from the included studies were extracted and evaluated for their quality and generalisability to the UK, based upon criteria developed by Drummond and colleagues.110 The studies identified are described in more detail in the following section.

A total of 236 potentially relevant references from our database underwent title and abstract screening. Of these, the full text versions (where available) of ten references were retrieved for screening, and two of these met the inclusion criteria (Figure 29).111,112 The characteritics of these studies are given in Table 25. Of the eight texts not included, four were abstracts with insufficient detail113-115 64 and four did not include long-term outcomes in their analysis68,71,84,116 (Appendix 6). The full data extraction forms for both of the included studies are shown in Appendix 7.

References for retrieval and screening n=10

Titles and abstracts inspected

n=236

Total identified from searching (after

de-duplication) n=236

Excluded

n=226

Excluded

n=8

Reasons for exclusion:

abstracts n=4;

outcome measure n=4.

Studies described in our review n=2

Figure Flow chart of identification of studies for inclusion in the review of cost-effectiveness

Table Characteristics of included economic evaluations

|  |  |  |
| --- | --- | --- |
| **Author** | **Hassan et al.**111 | **Kessler et al.**112 |
| Publication Year | 2010 | 2011 |
| Country | USA | USA |
| Funding source | Funding source not reported. | National Institutes of Health grant |
| Study type | Cost-effectiveness analysis | Cost-effectiveness analysis |
| Perspective | Societal | Not stated (assumed to be payer) |
| Study population | Hypothetical cohort of 100,000 50 year old persons in United States who underwent a colonoscopy for CRC screening. | Patients receiving a colonoscopy at a single-institution tertiary centre who had at least one polyp removed during colonoscopy, irrespective of indication. Population characteristics taken from a database of 10,060 consecutive colonoscopies from 1999 to 2004 |
| Intervention(s) | NBI versus colonoscopy versus no screening | No pathological examination of diminutive polyps (resect and discard) vs. submitting all polyps for pathological examination (submit all) |
| Intervention effect | Feasibility of 84% for rate of high confidence in differentiating between hyperplastic and adenomatous diminutive polys by using NBI without magnification. Sensitivity was 94% and specificity was 89%. | Endoscopic sensitivity for non-adenoma 90%;  Endoscopic sensitivity for adenoma 90%;  Proportion of diminutive polyps with advanced histology 0.6%;  Pathology sensitivity for large adenoma 100%;  Pathology sensitivity for diminutive and small adenoma 95%;  Pathology sensitivity for non-adenoma 100%. |
| Currency base | US dollars | US dollars |
| Model type, health states | Markov model with health states for: no colorectal neoplasia, diminutive (<= 5mm), small (6-9mm) or large (>=10 mm) adenomatous polyps; localised, regional, or distant CRC; and CRC related death. | Decision tree model |
| Time horizon | Lifetime horizon | Lifetime horizon |
| Base case results | Compared to standard colonoscopy, colonoscopy with NBI was $25 cheaper per person with no difference in life expectancy. | The net cost savings from forgoing histopathologic assessment was US$174.01. The expected increased benefit of the ‘submit all’ strategy was 0.17 days of life and the cost-effectiveness of the ‘submit all’ strategy compared to the ‘resect and discard’ strategy was US$377,460 per life year gained.  The number needed to harm because of perforation, major bleed or missed cancer was 7979, i.e., an absolute risk of 0.0125%. |

CRC - colorectal cancer

***Critical appraisal of the studies***

The assessment group critical appraisal of the identified studies by Hassan and colleagues111 and Kessler and colleagues112 are summarised in Table 26. Both studies report their methodology, assumptions and parameters clearly. Neither study included QALYs in their analysis and Kessler and colleagues did not include discounting. Hassan and colleagues did not present an incremental analysis, although it is possible to calculate this with the information provided.

Table Critical appraisal checklist for economic evaluations (based on Drummond et al110)

|  |  |  |
| --- | --- | --- |
| **Item** | **Hassan et al.**111 | **Kessler et al.**112 |
| 1. Is the decision problem (including interventions compared and patient group) relevant to the UK? | Yes | Yes |
| 2. Is the setting comparable to the UK? | Yes | Yes |
| 3. Is the analytical and modelling methodology appropriate? | Yes | Yes |
| 4. Are all the relevant costs and consequences for each alternative identified? | Yes | Yes |
| 5. Are the data inputs for the model described and justified? | Yes | Yes |
| 6. Are health outcomes measured in QALYs? | No | No |
| 7. Is the time horizon considered appropriate? | Yes | Yes |
| 8. Are costs and outcomes discounted? | Yesa | No |
| 9. Is an incremental analysis performed? | ?b | Yes |
| 10. Is uncertainty assessed? | Yes | Yes |
| Comments  a Discounted at 3% per annum, which differs from the National Institute for Health and Care Excellence reference case.  b Both colonoscopy and resect and discard appear to have been compared to no screening but no ICERs were calculated | | |

**Hassan and colleagues**

Hassan and colleagues111 developed a cost-effectiveness model to calculate the potential savings and drawbacks of a ‘resect and discard’ approach using NBI in a simulated colorectal cancer screening cohort. In the resect and discard approach, diminutive colorectal lesions (≤ 5mm), classified by endoscopy with high confidence, were not analysed by a pathologist. A Markov model was constructed with health states for no colorectal neoplasia, diminutive (<= 5mm), small (6-9mm) or large (>=10 mm) adenomatous polyps; localised, regional, or distant colorectal cancer; and colorectal cancer-related death. The resect and discard policy was instituted for all the cases in which a high confidence diagnosis was achieved by NBI. All diminutive polyps in which a high confidence diagnosis was not possible were removed and sent for formal histologic evaluation. The model assumed a screening strategy of colonoscopy every 10 years. After colonoscopy, patients received follow-up surveillance based upon the size and classification of the polyp(s).

Feasibility and accuracy of NBI without optical magnification in differentiating between diminutive adenomas and hyperplastic polyps were derived from three published series.13,71,74 Feasibility was defined as the rate of high confidence in differentiating between polyps. An 84% feasibility was assumed. The sensitivity and specificity for adenomas was 94% and 89%, respectively.

Costs were derived from Medicare reimbursement rates. No incremental cost for NBI was included because it was stated to be a standard feature in current generation colonoscopes. The cost of colonoscopy was $630, the cost of colonoscopy with polypectomy was $925, and pathologic examination was $102. Costs were also included for colorectal cancer treatment and adverse event costs, such as perforation and bleeding. Costs and life years were discounted at 3% per annum.

The discounted costs for the no screening strategy were $3390 per person over their lifetime (Table 27). The colonoscopy screening strategy reduced costs by $168 per person and the colonoscopy with resect and discard strategy reduced costs by a further $25 per person. Colonoscopy with or without resect and discard improved life expectancy by an average of 51 days per person compared with no screening. The study also extrapolated the results to the US population.

Table Cost and efficacy for the screening strategies of Hassan and colleagues

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No screening** | **Colonoscopy** | **Colonoscopy with resect and discard** |
| Cost/person | $3390 | $3222 | $3197 |
| Relative efficacy | - | 51 days / person | 51 days / person |

**Kessler and colleagues**

Kessler and colleagues112 developed a decision tree model to quantify the expected costs and outcomes of removing diminutive polyps with or without subsequent pathologic assessment. They compared two strategies: ‘submit all’ diminutive polyps (≤ 5 mm in size) to pathological examination compared to no pathological examination of diminutive polyps (‘resect and discard’). All other polyps were submitted for pathological examination for both strategies.

The decision model was populated with polyp frequencies based on a database of 10,060 consecutive patients who underwent colonoscopy for screening, surveillance or diagnostic indications. The decision model evaluated the frequency with which the surveillance follow-up (based on the most advanced polyp) matched that of the actual follow-up interval for the two strategies. Patients in the endoscopy database were distributed amongst four groups based on the characteristics that form the basis for follow-up. Group one consisted of people who had only one diminutive polyp. Group two had people who had two polyps, at least one of which was diminutive and the other not a large adenoma (≥10mm). In group three, people had at least three polyps at least one of which was diminutive and the others were not large adenomas. In group four people had at least one diminutive polyp, as well as one or more large adenoma(s) and could have any number of additional polyps. For each of the four groups, each patient’s most advanced polyp was either an advanced adenoma, a non-advanced adenoma or a non-adenoma.

The sensitivity and specificity of endoscopic and pathology assessment were based on the published literature.Costs were included for pathology, colonoscopy and colorectal cancer treatment. The cost of sending a polyp to pathology was US$103.87. Costs of colonoscopy, colonoscopic perforation and cancer treatment were obtained from the literature. The colonoscopy costs were US$1329 for diagnostic and US$2038 for therapeutic colonoscopies. The downstream costs and outcomes after the colonoscopy were obtained from a published discrete event simulation model of colorectal cancer screening and surveillance intervals.117 Discounting was not included in the model.

The submit-all strategy resulted in an incorrect surveillance interval 1.9% of the time, while the resect and discard strategy did so 11.8% of the time, with over half of the patients having only non-adenomatous polyps but scheduled for a 5 year, rather than a 10 year surveillance examination. The cost savings from forgoing pathologic assessment were US$210 per colonoscopy when diminutive polyps were removed, while the additional cost due to the incorrect surveillance interval was US$35.92. The net saving was US$174.01. The number needed to harm because of perforation, major bleed or missed cancer was 7979, i.e., an absolute risk of 0.0125%.

The expected additional benefit of the submit-all strategy was 0.17 days of life over the lifetime horizon and the incremental cost-effectiveness ratio (ICER) of the submit-all strategy compared to the resect and discard strategy was US$377,460 per life year gained.

Deterministic sensitivity analyses were conducted for the accuracy of the colonoscopy to detect adenomas and the proportion of diminutive polyps with advanced histology. The sensitivity analyses performed indicate that the error rate in assigning post-polypectomy surveillance intervals was most sensitive to the accuracy of endoscopic assessment of histology and to the proportion of diminutive polyps with advanced histology.

The authors concluded that endoscopic diagnosis of polyp histology during colonoscopy and forgoing pathologic examination would result in substantial upfront cost savings. Downstream consequences of the resulting incorrect surveillance intervals appear to be negligible.

***Summary of published economic evaluations***

The cost-effectiveness review of published economic evaluation for virtual chromendoscopy technologies found two relevant studies that were both published in the USA.111,112 The patient population differed between the two studies, Hassan and colleagues simulated a screening population (i.e. included patients who had no polyps identified by the colonoscopy) and Kessler and colleagues’ population had at least one diminutive polyp identified. Both studies compared a ‘resect and discard’ strategy to a ‘submit all’ (to histopathology) strategy to the whole colon, although Kessler and colleagues112 assumed that the resect and discard strategy would be used for all polyps, whilst Hassan and colleagues112 assumed that for some polyps it would not be feasible to use resect and discard (i.e. those characterised with low confidence). Neither studies used surveillance intervals for follow-up screening that correspond to those used in the UK.

The model structure differed between the two studies, Hassan and colleagues112 used a Markov model and Kessler and colleagues112 used a decision tree model. We consider that both approaches are appropriate. The cost saved per person varied between US$25111 and US$174 over the patient lifetime.112 The expected benefit of histopathology was 0.17 days of life in Kessler whilst Hassan assumed there was no difference in life expectancy between groups over the patient lifetime. The cost-effectiveness of the submit all strategy compared to resect and discard varied was US$377,460 per life year gained for Kessler and colleagues, whilst Hassan and colleagues were not able to calculate a value as there was no difference in the life expectancy between the submit all and resect and discard strategy. It is unclear how generalisable these results are to UK NHS as they have used non-UK resource costs and have not included QALYs.

***Review of information provided by Olympus to the National Institute for Health and Care Excellence: economic evaluation***

A budget impact model was supplied as part of the information provided by Olympus to the National Institute for Health and Care Excellence and the assessment group. The model has also recently been published by Solon and colleagues.116 This study did not meet our inclusion criteria for cost-effectiveness models of virtual chromoendoscopy because it did not include long-term health outcomes. However, we have provided a critical review of it as a supplement to our systematic review of cost-effectiveness studies as it has some relevance to the decision problem in this assessment.

**Modelling approach**

The analysis is a cost consequence and budget impact model that follows cohorts of UK patients who attend colorectal cancer screening. The population includes patients identified through the national screening programme as well as those attending for colonoscopic surveillance. The analysis is conducted from the perspective of the NHS in England. The model has a time horizon of seven years and in each year there is a new incident cohort of patients that undergo an endoscopy. The model includes a discount rate of 3.5% per year for costs and health outcomes. The model has a starting population of 550,925 attending an endoscopy test per year, to reflect the number of procedures conducted in 2012, and assumes an annual increase of 20% in the population expected to attend endoscopy each year. It was assumed that 82% of the installed endoscopy systems in England were manufactured by Olympus.

After undergoing endoscopy, patients are classified in three outcomes according to the number and size of polyps identified (no polyps; one of more polyps ≤5 mm but no polyps >5 mm; one or more polyps ≥ 5mm). For white light endoscopy (WLE), all polyps are resected and sent for histopathological examination. With NBI, for polyps ≤5 mm, the diagnosis of a proportion of polyps is assumed to be predicted with low confidence and they are sent for histological examination, whilst polyps will be left in situ if there is high confidence that they are non-neoplastic, otherwise they will be resected and discarded. Where polyps are resected, there is a risk of adverse events of bleeding and bowel perforation. The model calculates the number of true negatives, false negatives, true positives and false positives and the number of histological examinations, resects and adverse events for each cohort in each year.

**Critical appraisal of the model**

The assessment group critical appraisal of the Olympus economic model is summarised in Table 28. In general, the model is well reported although some aspects were reported in the economic model provided by Olympus (Appendix 8), rather than in Solon and colleagues.116 The time horizon is seven years but consists of seven yearly cohorts and no longer-term outcomes, such as QALYs, were modelled.

Table Critical appraisal checklist of economic evaluation (Questions in this checklist based on Drummond et al.110 and the National Institute for Health and Care Excellence reference case118

|  |  |  |
| --- | --- | --- |
|  | **Item** |  |
| 1 | Is there a clear statement of the decision problem? | Yes |
| 2 | Is the comparator routinely used in UK NHS? | Yes |
| 3 | Is the patient group in the study similar to those of interest in UK NHS? | Yes |
| 4 | Is the health care system comparable to UK? | Yes |
| 5 | Is the setting comparable to the UK? | Yes |
| 6 | Is the perspective of the model clearly stated? | Yes |
| 7 | Is the study type appropriate? | Yes |
| 8 | Is the modelling methodology appropriate? | Unclear |
| 9 | Is the model structure described and does it reflect the disease process? | Yes |
| 10 | Are assumptions about model structure listed and justified? | Yes |
| 11 | Are the data inputs for the model described and justified? | Yes |
| 12 | Is the effectiveness of the intervention established based on a systematic review? | Yes |
| 13 | Are health benefits measured in QALYs? | No |
| 14 | Are health benefits measured using a standardised and validated generic instrument? | No |
| 15 | Are the resource costs described and justified? | Yes |
| 16 | Have the costs and outcomes been discounted? | Yes |
| 17 | Has uncertainty been assessed? | Yes |
| 18 | Has the model been validated? | No |

**Clinical effectiveness**

The model parameters for the diagnostic accuracy of NBI, the feasibility of diagnosing diminutive polyps and adverse events were derived from a systematic literature review and are shown in Table 29.

Table Effectiveness parameters used in the Olympus economic model

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Source** |
| Patients with no polyps, % | 44% | Rastogi et al. (2012)119 |
| Patients with polyps ≤ 5mm, % | 38% | Rastogi et al. (2012)119 |
| Patients with polyps > 5mm, % | 18% | Rastogi et al. (2012)119 |
| Polyps that are adenomatous ≤ 5mm, % | 17% | Butterly et al. (2006)120 |
| Polyps that are adenomatous > 5mm, % | 10.1% | Butterly et al. (2006)120 |
| Diminutive polyp optical diagnosis feasibility rate | 75% | Kaltenbach et al. (2014)43 |
| Optical diagnosis sensitivity NBI | 93% | McGill et al.(2013)55 |
| Optical diagnosis specificity NBI | 83% | McGill et al.(2013)55 |
| Probability of hospitalisation for bleeding with polypectomy | 0.43% | Whyte et al. (2012)121 |
| Probability of perforation with polypectomy | 0.28% | Whyte et al. (2012)121 |

**Estimation of costs**

The model includes the costs incurred by the NHS, including equipment, maintenance, training, consumables, staff, endoscopy and histological examination costs and hospital costs for managing adverse events. Unit costs of resources were taken from a variety of sources including NHS Reference costs,122 PSSRU,123 and the company’s own prices. The costs used in the model are shown in Table 30.

The company’s list price for NBI systems is £40,395. The model assumes that at the start of the first year 82% of hospitals currently use Olympus systems, of which 95% are capable of NBI, i.e. 78% of hospitals use NBI. Of those hospitals with Olympus equipment, 50% of hospitals that do not have NBI capable systems will upgrade in year one and a similar number in each subsequent year. Of those hospitals with Olympus equipment, 50% have NBI-capable endoscopes in place in the first year. Of those hospitals with Olympus equipment, that do not have NBI-capable endoscopes, 14% will upgrade in year one and a similar number will upgrade in each subsequent year. For NBI, two training days per endoscopist per year are required, while no additional training is required for WLE.

Staff costs for colonoscopy include costs for administration, nurse and consultant contact time and are based upon a micro-costing study of a Canadian hospital.124 The consumables for biopsy are snares and forceps. The assessment group notes that consumables and staff costs would normally be included within the NHS Reference costs and do not therefore need to be included separately.

Table Cost parameters used in the Olympus economic model

| Input parameter | Value | Source |
| --- | --- | --- |
| Unit cost per system NBI | £40,395 | Olympus list price |
| Unit cost per scope NBI | £38,660 | Olympus list price |
| Training cost per year NBI | £2,272 | Olympus list price |
| Maintenance cost NBI system | £3,525 | Olympus list price |
| Maintenance cost NBI scopes | £4,805 | Olympus list price |
| NHS Tariff for colonoscopy - with biopsy | £522 | Monitor 2014 - HRG tariff FZ51Z |
| NHS Tariff for colonoscopy - without biopsy | £437 | Monitor 2014 - HRG tariff  FZ52Z |
| Cost per biopsy | £82 | Unpublished data obtained from University College London Hospitals, Plymouth Hospital NHS Trust and South Devon Healthcare NHS Foundation Trust |
| Number of biopsies per exam | 1.35 | Assumption based on data reported in Lee et al, 2012 |
| Cost per hospital bleed | £318 | Monitor 2015-6 - HRG tariff FZ38F |
| Cost per perforation event | £2,211 | Monitor 2015-6 - HRG tariff GB01B |
| Unit cost per hour for administration & support | £23 | PSSRU 2014 |
| Hours per test for administration & support | 0.30 | Modified from assumptions reported in Sharara et al. 2008124 |
| Unit cost per hour nurse non-contact time | £41 | PSSRU 2014 |
| Hours per test for nurse non-contact time | 0.42 | Modified from assumptions reported in Sharara et al. 2008124 |
| Unit cost per hour of consultant time | £142 | PSSRU 2014 |
| Hours with consultant, excluding procedure | 0.50 | Modified from assumptions reported in Sharara et al. 2008124 |
| Length of procedure time in hours with NBI | 0.30 | Bisschops et al. 2012125 |
| Length of procedure time in hours with comparator | 0.30 | This input varies where options are selected |
| Unit cost per hour nurse contact time | £100 | PSSRU 2014 |
| Snares - cost per pack | £240 | Olympus list price |
| Snares - number per pack | 20 | Market data provided by Olympus |
| Forceps - cost per pack | £210 | Olympus list price |
| Forceps - number per pack | 10 | Market data provided by Olympus |

**Results**

The results for the outcomes from the model are shown in Table 31. Over seven years NBI reduced the incidence of colonoscopy-related adverse events by 32% and the frequency of histopathological examination by 39%.

Table Outcomes from the Olympus economic model

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **NBI** | **WLE** | **% Change** |
| True negatives | 5,713,178 | 5,933,416 | -3.71% |
| False negatives | 1,596 | - | N/A |
| True positives | 148,296 | 149,893 | -1.07% |
| False positives | 220,238 | - | N/A |
| Histopathology exams | 2,065,058 | 3,406,653 | -39.38% |
| Adverse events | 16,376 | 24,187 | -32.29% |

The cost over seven years for NBI is predicted to be £3,112 million and for WLE is £3,253 million, i.e. a saving of £141 million.

Deterministic sensitivity analyses were included in the model by varying the model parameters by +/-10%. The sensitivity analysis shows the effect of the parameters on the total difference in costs between NBI and WLE. The costs of colonoscopy with and without biopsy have the greatest impact on model results. The study also conducted an analysis reducing the cost of biopsy, which showed there was still a net cost saving with NBI even when the biopsy cost was reduced to zero.

* 1. Independent economic evaluation

As described in Section ‎2, the decision problem for this diagnostic assessment is to assess the cost-effectiveness of real-time optical assessment of diminutive colorectal polyps in the English NHS.

We therefore conducted an economic evaluation to evaluate costs and outcomes of virtual chromoendoscopy. The economic evaluation takes the form of a cost-utility model informed by the systematic review of cost-effectiveness studies, the economic evaluation by Olympus, targeted literature searches and, where necessary, expert opinion. The economic evaluation uses the diagnostic accuracy for virtual chromoendoscopy from the meta-analyses reported in section ‎4.

* 1. Methods for economic analysis

The decision problem

The patient population in our base case analysis is people referred to colonoscopy after participating in a bowel cancer screening programme (referred to as the **screening population**). We included in scenario analyses two other patient populations of relevance to the decision problem for this assessment: people offered colonoscopic surveillance because they had previously had adenomas removed (**surveillance population**); and people referred for colonoscopy by a GP because of symptoms suggestive of colorectal cancer (**symptomatic population**).

For the purposes of the economic analysis, we only include patients with at least one diminutive polyp and exclude patients with one or more non-diminutive polyp. The scope for this assessment excludes use of virtual chromoendoscopy for real-time assessment of non-diminutive polyps (>5mm), though VCE might be considered for use in the assessment of diminutive polyps in patients who also have non-diminutive polyps. In practice, patients do have a mixture of polyps of different sizes. Although most polyps are diminituive, patients are assigned to surveillance intervals according to their most advanced polyp. However, we could not identify data on the mix of different sized polyps in patients or how they affect the allocation to surveillance interval. Additionally, all data in the model on adenoma and cancer risk is based on data that averages risk across adenoma sizes.

Further, the model does not differentiate between the type of polyp, such as depressed polyps or sessile serrated polyps. Sessile serrated polyps are relatively uncommon and no diagnostic accuracy data were available for diminutive sessile serrated polyps from our systematic review of diagnostic studies (Section ‎4).

For the base case analysis in our economic evaluation, we compare strategies using virtual chromoendoscopy technologies (NBI, i-scan and FICE) with a histopathology assessment strategy. For the comparator **histopathology strategy**, we assume that all polyps are resected and sent for histopathology, and that subsequent screening and surveillence invitations are based on the histopathology results, which are assumed to be 100% accurate.

We refer to the virtual chromoendoscopy strategy used in our base case analysis as the **VC strategy**; it has the following characteristics:

* Diminutive polyps in the whole colon are optically characterised using virtual chromoendoscopy
* Diminutive polyps characterised with high confidence as adenomas are resected and discarded
* Diminutive polyps characterised with high confidence as hyperplastic are left in situ
* Any polyps that cannot be characterised with high confidence are resected and sent to histopathology

The VC strategy is based upon the Detect InSpect ChAracterise Resect and Discard (DISCARD) strategy described in Ignjatovic and colleagues71 and then subsequently adapted in the two economic models identified by our systematic review of economic evaluations.111,112 Ignjatovic and colleagues’ study71 was one of the first to evaluate a resect and discard strategy, and they proposed that polyps <10mm in size should be characterised, and if appropriate be discarded or left in situ without histopathology. Subsequent studies and guidance have modified the DISCARD strategy to apply to only diminutive polyps (≤5 mm). The NICE scope, ESGE guidelines,43 both economic evaluations identified through our systematic review, and our model limit the VC strategy to diminutive polyps.

Our VC strategy does differ from the DISCARD strategy in the way that hyperplastic polyps are dealt with in the proximal colon (see Figure 3 on page 35 above). In the base case analysis, the model does not differentiate between diminutive hyperplastic polyps found in the rectosigmoid colon or other parts of the colon, because the best available diagnostic data from our systematic review was based on polyps in the whole colon. However, we have conducted scenario analyses (section ‎5.5.2) using what we refer to as the **DISCARD strategy**, which has the following characteristics:

* Any polyp assessed with low confidence is resected and sent to histopathology
* Diminutive polyps in the whole colon characterised with high confidence as adenomas are resected and discarded
* Diminutive polyps in the proximal colon characterised with high confidence as hyperplastic are resected and discarded
* Diminutive polyps in the rectosigmoid colon characterised with high confidence as hyperplastic are left in situ

We assessed each of the virtual chromoendoscopy based strategies (VC and DISCARD) for each of the three technologies (NBI, i-scan and FICE). In addition, we conducted a scenario analysis using the post hoc pooled meta-analysis sensitivity and specificity estimates for the virtual chromoendoscopy technologies (Section ‎4.1.2).

Following colonoscopy and receipt of histopathology results, patients are assigned a surveillance interval based on their estimated level of risk (see Figure 30). The risk classification of patients used corresponds to British guidelines41 for determining surveillance intervals following identification of exclusively diminutive adenomas at colonoscopy: low risk (0-2 adenomas); intermediate risk (3-4 adenomas), and high risk (5 or more adenomas).



Figure adapted from ‘Public health functions to be exercised by NHS England: Service specification No.26, Bowel Cancer Screening Programme’126

Figure NHS Bowel Cancer Screening Pathway (with endoscopy policies)

There are four main implications of using a virtual chromoendoscopy strategy (VC or DISCARD) rather than the histopathology strategy:

1. **Initial costs:** Most hospitals already have equipment capable of VCE. There would be additional training costs for endoscopists to use this technology, but conversely the cost of polypectomies and histopathology tests would be reduced. Thus the net effect on the cost of initial diagnosis and management (colonoscopy, polypectomy and histopathology) may be positive or negative.
2. **Hyperplastic polyps resected**: The number of hyperplastic polyps unnecessarily resected and hence the numbers of polypectomy-related adverse events, such as bleeding and bowel perforation, will be reduced. Some hyperplastic polyps will still be resected, because they are not assessed with high confidence or are mischaracterised as adenomas (false positives). Adverse events are associated with a mortality risk, reduced quality of life and costs to the health service.
3. **Missed adenomas**: However, some polyps will be mischaracterised as hyperplastic when they are adenomas (false negatives). Such errors will mean that some adenomas will be left in situ, leading to a small increase in the incidence of colorectal cancer, with associated QALY loss and healthcare costs.
4. **Incorrect follow up**: Some patients may be assigned to the wrong follow up interval (according to the BCSP guidelines, Figure 30): either too long an interval if one or more adenomas are missed (false negatives); or too short an interval if one or more hyperplastic polyps are characterised as adenomas (false positives). In general, a shorter follow up interval will be beneficial for the patient, due to the reduced risk or earlier detection of cancer. However, for patients at very low risk of colorectal cancer, the potential harm from polypectomy-related adverse events could offset these benefits. The incremental cost to the health service of a shorter follow up interval may, in principle, be positive or negative: since increased costs of screening or surveillance may, to some extent, be offset by cost savings from avoided cancer treatment.

The model estimates the proportion of patients likely to experience these various risks, and hence the expected costs and QALYs associated with the alternative colonoscopy strategies.

Model structure

The model consists of a decision tree for patients undergoing colonoscopy. The tree estimates the short term costs and outcomes for the defined population under each decision strategy, from the time when patients are identified as potential candidates for use of virtual chromoendoscopy, up to the time when any polyps identified as adenomas have been removed and patients have been assigned to a follow-up policy. Long-term costs and QALY outcomes at the endpoints of the decision tree were estimated from an existing model: the School of Health and Related Research (ScHARR) Bowel Cancer Screening (SBCS) model, developed by Whyte and colleagues.121 We chose to use the SBCS model, rather than to develop a new one, because it is a long-standing model, that has been validated, and which was used to inform the introduction of the national bowel cancer screening programme. The SBCS model was adapted for this current assessment, with updated parameters where possible. It was run independently, and the SBCS cost and QALY estimates for various subgroups of patients were entered as parameters at the endpoints of the decision tree model. The structures and assumptions of the decision tree and SCBS models are described below. Input parameters for both models are then discussed in Section ‎5.4.

* + - 1. The decision tree

The decision tree model compares the virtual chromoendoscopy strategies (VC with each of the teachnologies NBI, i-scan, FICE in the base case) with a histopathology strategy for a cohort of patients (the screening population in the base case). The model adopts a life time horizon and an NHS and personal and social services perspective.

Patients enter the model at colonoscopy, having had at least one diminutive polyp, and no non-diminutive polyps, identified. The cohort is divided into four risk categories, based on the number of adenomas that they have:

* No adenomas
* Low risk (LR): 1-2 adenomas
* Intermediate risk (IR): 3-4 adenomas
* High risk (HR): 5 or more adenomas

The model then calculates the proportion of patients in each category expected to have the correct diagnosis and treatment, and the proportions expected to be diagnosed and treated incorrectly. There are essentially three types of error that can occur: patients might have one or more hyperplastic polyp misclassified as an adenoma and unnecessarily resected; they may have one or more adenoma misclassified as a hyperplastic polyp and left in situ; and/or they may be assigned to an incorrect surveillance interval – either too long or too short. The resulting permutations of diagnostic outcomes for patients are illustrated in Figure 31. It can be seen that there are six main patient outcomes, which are also defined in Table 32.

Table Definitions of diagnostic outcomes for patients

|  |  |  |  |
| --- | --- | --- | --- |
| Patient outcomes | | Interpretation | Surveillance interval assigned |
| CD | Correct diagnosis | All polyps correctly classified (as either adenomas or hyperplastic polyps) | Correct |
| MAC | Missed adenoma(s) correct surveillance | One or more adenomas identified incorrectly as hyperplastic polyps and left in situ | Correct |
| MAI | Missed adenoma(s) incorrect surveillance | One or more adenomas identified incorrectly as hyperplastic polyps and left in situ | Incorrect – too long |
| HPRC | Hyperplastic polyp(s) resected correct surveillance | One or more hyperplastic polyps identified incorrectly as adenomas and resected | Correct |
| HPRI | Hyperplastic polyp(s) resected incorrect surveillance | One or more hyperplastic polyps identified incorrectly as adenomas and resected | Incorrect – too short |
| MAHPR | Missed adenoma(s) and hyperplastic polyp(s) resected | One or more hyperplastic polyps identified incorrectly as adenomas and resected and  One or more adenomas identified incorrectly as hyperplastic polyps and left in situ | Correct a |

a The probability that a patient who has both false positive and false negative test results is given the wrong surveillance interval is very small, as this would require a total of three or more errors (one false positive and two false negatives, or vice versa).

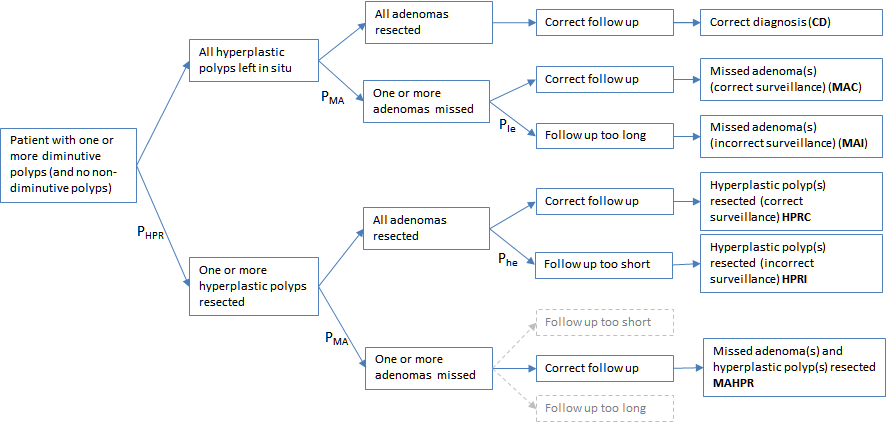


Figure Decision tree showing diagnostic outcomes for patients

The probability of these different outcomes depends on the number of polyps and adenomas that the patient has, the diagnostic accuracy of the colonoscopy technology, and the policies for resecting polyps and assigning surveillance intervals.

In general, if the actual number of adenomas is at the higher end of the risk classification range, then if the patient has one or more hyperplastic polyps identified incorrectly as adenomas, they may be given a shorter surveillance interval than is appropriate. Similarly, if the actual number of adenomas is at the lower end of the risk classification range, then if the patient has one or more adenomas identified incorrectly as hyperplastic polyps and left in situ, they may be given a longer surveillance interval than is appropriate.

Some outcomes are not possible for particular groups of patients: for example, a patient with one hyperplastic polyp and one adenoma (LR) cannot be assigned an incorrect surveillance interval, since even if the hyperplastic polyp is mistaken for an adenoma, they would still be placed in the LR group and be invited (correctly) for routine screening. Other outcomes will be very improbable for some patients: for example, a patient with 9 adenomas (HR) is very unlikely to be diagnosed with less than 5 adenomas, and so is unlikely to be assigned to a surveillance interval that is too long.

It is possible that patients could simultaneously have one or more hyperplastic polyp misdiagnosed as an adenoma (FP) and one or more adenoma misdiagnosed as a hyperplastic polyp (FN). If so, the patient would be at risk of harm from the unnecessary resection(s) and increased risk of cancer due to the adenoma(s) left in situ. However, it is unlikely that they would be assigned to an incorrect surveillance interval, since the errors for individual polyps would be likely to cancel out.

The mathematics behind the estimation of outcome probabilities for patients from polyp-level diagnostic accuracy estimates is explained in section ‎5.3.2.2 below. But first we continue the overview of the decision tree model, and explain how it links to long-term outcomes from the SBCS model.

Under the histopathology strategy, all patients are assumed to receive the correct diagnosis (Table 33). All polyps including adenomas are resected, so no adenomas are left in situ, and patients are assigned to the correct follow up strategy: routine invitation to screening for those with 0-2 adenomas, three-yearly surveillance for those with 3-4 adenomas, and annual surveillance for those with 5 or more adenomas. The model calculates the resources required for histopathology and polypectomy and the number of adverse events that result from polypectomies, with associated treatment costs and disutilities. Long-term outcomes associated with each diagnostic outcome are taken from the SBCS model with no adenomas left in situ and all patients assigned to the correct follow up. The SBCS model includes higher adenoma incidence rates for patients who have had adenomas resected than for patients who started without adenomas (normal epithelium), and the rate of recurrence of adenomas is higher for patients who were initially at higher risk. Cancer incidence, and hence costs and outcomes in the SBCS model, also depend on the surveillance interval assigned. A detailed description of the SBCS model is provided below in Section ‎5.3.2.3.

Table 33 Diagnostic outcomes by initial risk status: Histopathology strategy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Initial risk (adenomas) | Patient outcome | Hyperplastic resected | Adenomas missed | Surveillance interval | Initial SBCS state |
| LR (0) | CD | All | None | Correct | Normal (screening) |
| LR (1-2) | CD | All | None | Correct | LR all resected (screening) |
| IR (3-4) | CD | All | None | Correct | IR all resected (3-yearly) |
| HR (5+) | CD | All | None | Correct | HR all resected (annual) |

With VC, errors in characterisation of polyps are possible, and hence patients may be left with one or more adenomas in situ (due to false negatives), and/or have hyperplastic polyps unnecessarily resected (due to false positives). Errors in polyp characterisation with VC might also cause patients to be allocated to the wrong follow up strategy – with either too long or too short an interval. The diagnostic outcomes for patients under the VC strategy are shown in Table 34. Outcomes that are impossible or very unlikely are omitted from this table.

For patients without any adenomas, there are only two possible outcomes: they may have a correct diagnosis and have no polyps resected (CD); or they may have one or more hyperplastic polyps removed unnecessarily (HPRC). In either case, patients with no adenomas are very unlikely to be assigned the wrong follow up: the probability of the three or more FP results that would be required for them to be incorrectly assessed as IR is very low. Costs and outcomes for this group are therefore taken from the results for patients starting in SBCS model in the ‘normal epithelium’ health state and following routine screening. There are five possible diagnostic outcomes for patients with 1-2 adenomas. They may be correctly diagnosed (CD); have one or more adenoma missed, but no resections of hyperplastic polyps and be assigned correctly to routine screening (MAC); have no adenoma missed but one or more hyperplastic polyps resected, either with the correct follow up of routine screening (HPRC) or unnecessary 3-yearly surveillance (HPRI); or they may have one or more adenoma missed and also one or more hyperplastic polyp resected with the correct follow up (MAHPR). Patients in this group start in the SBCS model in the ‘post polypectomy (low risk adenomas removed)’ health state or in the ‘low risk adenomas’ health state (1-2 diminutive adenomas in situ). All patients in this group will be invited for routine screening, except those with one or more FP results who are misclassified as IR. Finally, patients with three or more adenomas (IR or HR) have all possible outcomes illustrated in Figure 31. We assume that patients in this group with one or more missed adenomas start in the ‘LR adenomas’ health state in the SCBS model, with 1-2 adenomas in situ: although it is possible that patients could have 3 or more adenomas missed, this is very unlikely.

Table Diagnostic outcomes by initial risk status: VC strategy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Initial risk (adenomas) | Patient outcome | Hyperplastic resected | Adenomas missed | Follow up interval | Initial SBCS state |
| LR (0) | CD | None | - | Correct | Normal (screening) |
| HPRC | One or more | - | Correct | Normal (screening) |
| LR (1-2) | CD | None | None | Correct | LR all resected (screening) |
| MAC | None | One or more | Correct | LR adenomas (screening) |
| HPRC | One or more | None | Correct | LR all resected (screening) |
| HPRI | One or more | None | Too short | LR all resected (3-yearly) |
| MAHPR | One or more | One or more | Correct | LR adenomas (screening) |
| IR (3-4) | CD | None | None | Correct | IR all resected (3-yearly) |
| MAC | None | One or more | Correct | LR adenomas (3-yearly) |
| MAI | None | One or more | Too long | LR adenomas (screening) |
| HPRC | One or more | None | Correct | IR all resected (3-yearly) |
| HPRI | One or more | None | Too short | IR all resected (annual) |
| MAHPR | One or more | One or more | Correct | LR adenomas (3-yearly) |
| HR (5+) | CD | None | None | Correct | HR all resected (annual) |
| MAC | None | One or more | Correct | LR adenomas (annual) |
| MAI | None | One or more | Too long | LR adenomas (3-yearly) |
| HPRC | One or more | None | Correct | HR all resected (annual) |
| HPRI | One or more | None | Too short | HR all resected (annual) |
| MAHPR | One or more | One or more | Correct | LR adenomas (annual) |

* + - 1. Estimating patient outcome probabilities from polyp-level diagnostic accuracy

***Probability of test results for an individual polyp***

For the individual polyp, there are four possible VCE test results (TP, FP, FN and TN). The probability of these outcomes can be calculated as a function of the proportion of polyps that are adenomas (p), and the sensitivity (Se) and specificity (Sp) of the test, as shown in Table 35.

Table Virtual chromoendoscopy results for an individual polyp

|  |  |  |  |
| --- | --- | --- | --- |
| Polyp results | | Interpretation | Probability |
| TP | True positive | Adenoma correctly classified | P(TP) = p . Se |
| FP | False positive | Hyperplastic polyp identified incorrectly as an adenoma | P(FP) = (1-p) . (1-Sp) |
| FN | False negative | Adenoma identified incorrectly as a hyperplastic polyp | P(FN) = p . (1-Se) |
| TN | True negative | Hyperplastic polyp correctly classified | P(TN) = (1-p) . Sp |

p = proportion of polyps that are adenomas;   
Se = sensitivity of the VCE test (probability that an adenoma is correctly identified); and   
Sp = specificity of the VCE test (probability that a hyperplastic polyp is correctly identified).

***Probability of test results for multiple polyps***

For patients with more than one polyp, the probabilities of different combinations of test results can be estimated using the binomial distribution. For example, the probability that a patient with n polyps has k false positive test results is:

P(k FP) = P(FP)k (1 - P(FP))(n-k)

This formula is used in the decision tree model to estimate the probability of the six main diagnostic outcomes shown in Figure 31 and Table 32. This approach does require an assumption that the test results for individual polyps within a patient are independent of one another: thus, for example, the probability that an individual polyp gives a FP test result is assumed to be constant, regardless of whether other polyps in the patient have given an FP result. In practice, the types of polyp within a patient are likely to be clustered, however we have not identified any data to quantify the extent of any such clustering.

***Probability that one or more hyperplastic polyps are misidentified as adenomas***

The probability that one or more hyperplastic polyps are incorrectly identified as adenomas in a patient with n polyps is:

P(one or more FP in a patient) = 1 - P(no FP in a patient, k=0)

= 1 - P(FP)0 (1 - P(FP))(n-0)

= 1 - (1 - P(FP))n

In the cases where one or more polyp is assessed with low confidence (lc is proportion of polyps assessed with low confidence), the above formula can be generalised to:

P(one or more FP in a patient) = 1 - (1 - P(FP))n(1-lc)

***Probability that one or more adenomas are missed***

In a similar way, the probability that one or more adenomas are incorrectly identified as hyperplastic polyps is:

P(one or more FN in a patient) = 1 - (1 - P(FN))n(1-lc)

Or, in the cases wherethe DISCARD strategy is used, and the proportion of polyps in the proximal region is px:

P(one or more FN in a patient) = 1 - (1 - P(FN))n(1-lc)(1-px)

***Probability of correct / incorrect follow up intervals***

Whether patients are given incorrect follow up depends on their actual number of adenomas and the number of FP and FN results. Thus, a patient with five adenomas, who should be invited for annual surveillance, might be mistakenly invited for colonoscopy only once every three years if one or more adenoma was missed. Estimating the probabilities for every possible combination of adenomas, FP and FN results is complicated. However, the probability of being given the wrong surveillance interval is very low for some patients. For example, patients with no adenomas would need to have three more FP results than FN results, before they would move into the range where they might be offered three-yearly surveillance. Similarly, patients with seven adenomas would need three or more FN results than FP results to move from the annual to three-yearly surveillance category. Given the multiplicative nature of the binomial formula, and relative rarity of FP and FN errors, such outcomes are very unlikely. We therefore made a simplifying assumption: that the probability of three or more errors in polyp characterisation (FP and/or FN) within a patient is negligible. .

For each risk category, we estimated the proportion of patients who have the number of adenomas corresponding to the lower and higher ends of the classification range as,

le = % patients at the lower end / % patients in risk classification

he = % patients at the higher end / % patients in risk classification

The probability of patients having one or more missed adenomas and being assigned to an incorrect follow up strategy (too long an interval) is:

P(one or more missed adenoma in a patient and incorrect surveillance) = Ple . PMA

Similarly, the probability of patients having one or more hyperplastic polyp misclassified as an adenoma and being assigned to an incorrect strategy (too short an interval) is:

P(one or more MA in a patient and incorrect SI) = Phe. PHPR

The probability calculations for the six patient outcomes are summarised in Table 36.

Table Summary of probability calculations for diagnostic outcomes

|  |  |  |  |
| --- | --- | --- | --- |
| Patient outcome | Interpretation | Follow up interval | Probability |
| CD | Correct diagnosis | Correct | 1 – P(MAC) – P(MAI) – P(HPRC) – P(HPRI) – P(MAHPR) |
| MAC | Missed adenoma (correct surveillance) | Correct | (1-le).(1 - (1 - P(FN))n(1-lc)(1-px)) |
| MAI | Missed adenoma (incorrect surveillance) | Incorrect – too long | le. (1 - (1 - P(FN))n(1-lc)(1-px)) |
| HPRC | Hyperplastic polyp resected (correct surveillance) | Correct | (1-he). (1-(1- P(FP))n(1-lc) ) |
| HPRI | Hyperplastic polyp resected (incorrect surveillance) | Incorrect – too short | he. (1-(1- P(FP))n(1-lc) ) |
| MAHPR | Missed adenoma, hyperplastic polyp resected | Correct | P(FP).P(FN).(1-P(FP)-P(FN))(n-2) |

* + - 1. SBCS Markov model

The ScHARR Bowel Cancer Screening (SBCS) model121 describes the development of adenomas and colorectal cancer and subsequent disease progression for the general population of England eligible for bowel cancer screening. It was developed by ScHARR for the NHS Bowel Cancer Screening Programme. The model is a ‘Markov-type’ health state transition model, that takes a cohort approach (rather than individual-level simulation). It estimates QALYs and costs for a cohort of 65-year-olds at risk of developing colorectal cancer over a lifetime horizon and using an annual cycle length. Costs were estimated from the perspective of the English NHS, and a discount rate of 3.5% was applied to costs and QALYs. The basic model structure consists of a natural history model; and a screening and surveillance pathway.

The basic natural history model is illustrated in Figure 32. This shows the expected progression of adenomas and CRC in the absence of an active screening and surveillance programme.

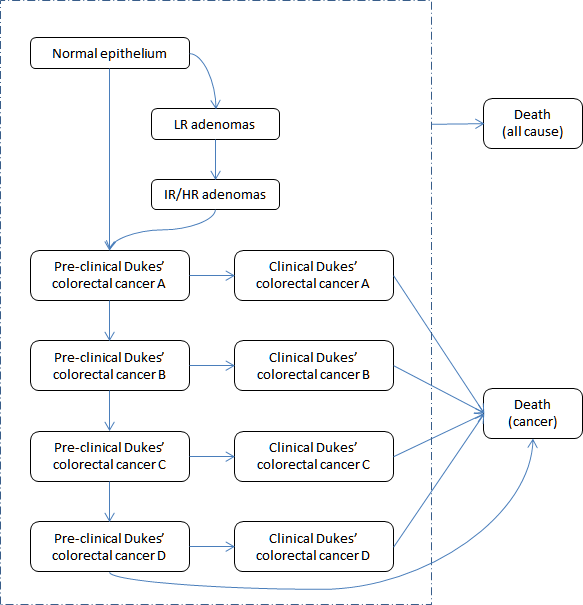


Figure SBCS natural history model

Adapted from Whyte and colleagues127

Patients start in one of the pre-cancer health states: normal epithelium (no adenomas); LR adenomas; or IR/HR adenomas. Over time, they may progress through the adenoma-cardinoma route: from normal epithelium to LR adenomas, to IR/HR adenomas, and to pre-clinical Dukes’ stage A CRC. It is also possible for patients to transition directly from normal epithelium to pre-clinical stage A CRC (*de novo* cancers). Pre-clinical cancer progresses through the stages, from A to B to C to D, but at some time it is likely to be diagnosed, through chance detection or symptomatic presentation, at which time the patient moves to the related ‘clinical’ cancer stage. Progression through the clinical cancer stages is not modelled, instead a stage-specific cancer survival rate is applied. It is also possible for patients with undiagnosed stage D cancer to be fatal. Patients can die from other causes from any of the health states.

The SBCS model was designed to evaluate alternative active screening and surveillance programmes. The post-screening surveillance pathway is illustrated in Figure 33.

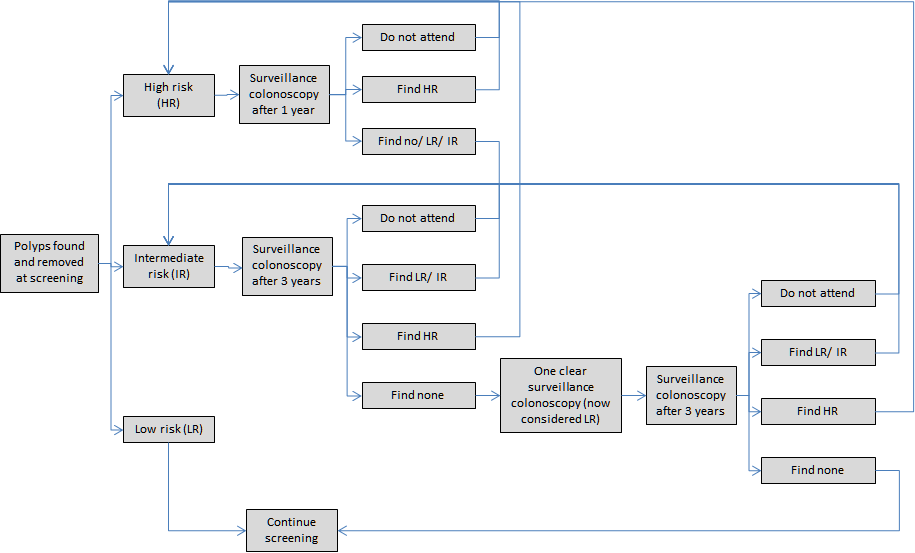


Figure SBCS Surveillance colonoscopy pathway

This shows the assumptions built in to the SBCS model about how patients would be followed up under BSG guidelines, according to findings at an initial colonoscopy after a positive screening result, which reflects the starting point from the end of our decision tree for our base case screening population. Patients assessed to be at low risk following an initial colonoscopy (0-2 diminutive adenomas in our population), or with no adenomas at two successive three-year surveillance colonoscopies, are assumed to be invited for routine screening. The screening pathway in the version of the SBCS model used to generate cost and QALY estimates for the VCE model was chosen to reflect the current NHS Bowel Cancer Screening Programme, with the offer of a home FOBT every 2 years for all men and women aged 60 to 74, and invitation for colonoscopy for patients with an abnormal screening test.

In the SCBS model, colonoscopy is assumed to be standard colonoscopy without virtual chromoendoscopy. However, the model does assume less than perfect sensitivity of colonoscopy for detecting adenomas: 0.77 for LR adenomas and 0.98 for IR/HR adenomas. It also assumes that the cost of histopathology is incurred only for adenomas, a mean of 1.9 per person undergoing colonoscopy. Thus the cost and accuracy of colonoscopy in the SCBS model is possibly more reflective of VCE than with standard colonoscopy.

The simple natural history diagram in Figure 32 does not show all transitions in the SBCS model. In particular, it omits recurrence of adenomas and cancer incidence for patients who have had adenomas removed at colonoscopy. These additional transitions are illustrated in Figure 34.

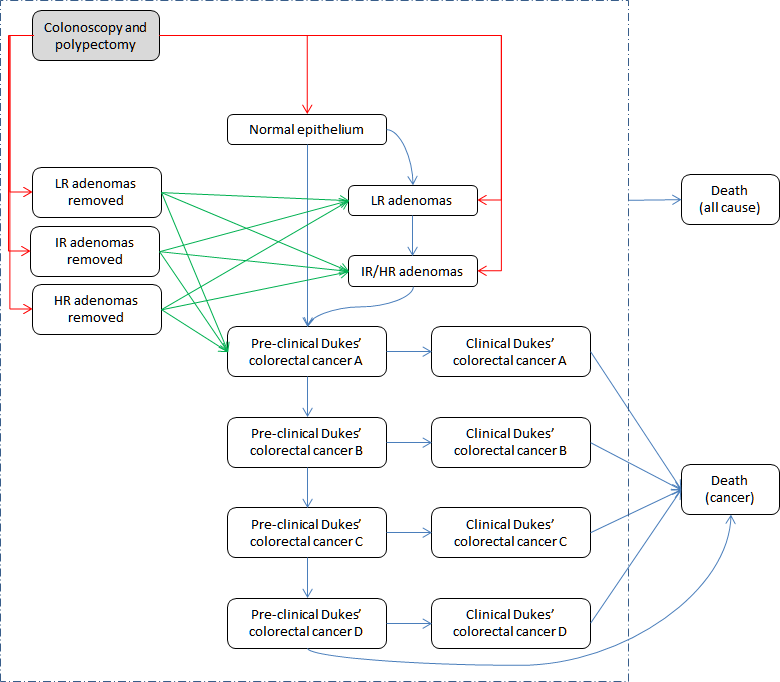


Figure SBCS adenoma recurrence following polypectomy

Following colonoscopy, patients enter the following health states in the SBCS model: patients who started with no adenomas go to the ‘normal epithelium’ state; patients with 1-2 adenomas left in situ, go to ‘LR adenomas’; those with 3 or more adenomas left in situ go to ‘IR/HR adenomas’; and patients who have all had adenomas resected go to the LR, IR or HR adenomas removed states, depending on their initial risk level. Subsequently, patients who have had all adenomas removed may have a recurrence of LR or IR/HR adenomas, and they also have a small chance of ‘de novo’ cancer, transitioning directly to pre-clinical Dukes’ stage A CRC.

Thus, the costs and QALYs for the endpoints of our decision tree were calculated by running the SBCS model with a cohort of 65 year old patients starting in each of the post-colonoscopy health states (normal epithelium, LR adenomas removed, IR adenomas removed, HR adenomas removed, LR adenomas and IR/HR ademomas). The model was run for each possible post-colonoscopy state three times, assuming routine screening, three-yearly surveillance and annual surveillance in turn. Several updates were made to the SBCS model for these analyses. The input parameters are described in section ‎5.4. Screening and treatment costs were inflated or updated where appropriate (Table 41 and Table 42). Analyses were run assuming the average number of adenomas present in patients with at least one adenoma was 1.9, although the SBCS model does not explicitly simulate the number of polyps. The final cost and QALY estimates from the SBCS model that were used in our decision tree analysis are shown below in Table 46.

**Evaluation of uncertainty**

The evaluation of the cost-effectiveness of virtual chromoendoscopy technologies is based on uncertain information about variables such as the diagnostic accuracy, polyp demographics, HRQoL and resource use. This uncertainty was evaluated using deterministic and probabilistic sensitivity analyses (PSA). One-way deterministic sensitivity analyses were conducted to evaluate the influence of individual parameters on the model results and to test the robustness of the cost-effectiveness results to variations in the structural assumptions (section ‎5.5.2.1).

Multi-parameter uncertainty in the model was addressed using PSA (section ‎5.5.2.3). In the PSA, probability distributions are assigned to the point estimates used in the base case analysis. The model is run for 5000 iterations, with a different set of parameter values for each iteration, by sampling parameter values at random from their probability distributions. The uncertainty surrounding the cost-effectiveness of each treatment is represented using a cost-effectiveness acceptability curve (CEAC) according to the probability that the intervention will be cost effective at a particular willingness to pay threshold. Appendix 9 reports the parameters included in the PSA, the form of distribution used for sampling each parameter, and the upper and lower limits assumed for each variable.

The results of the PSA should be treated with some caution, however, since it does not reflect some important sources of uncertainty or correlations between model parameters. Firstly, we note that the PSA does not integrate uncertainty over the long-term impact of diagnostic errors on patient outcomes and costs, since we could not obtain correlated samples of cost and QALY outputs from the SBCS model. The PSA also omits correlations between sensitivity and specificity estimates from our bivariate meta-analysis. Statistical advice to the team, indicated that if no threshold effect could be demonstrated between diagnostic sensitivity and specificity of virtual chromoendoscopy, then modelling these parameters as uncorrelated in PSA would have little effect on their uncertainty in comparison to modelling them allowing for correlation. In our meta-analyses (Section ‎4.1.2), we found that there was no significant evidence of a threshold effect. Therefore, for the PSA we have varied sensitivity and specificity independently. It is most likely that the the consequence of these omissions is that the PSA under-estimates overall uncertainty over the cost-effectiveness of the VCE strategies. In addition, there are uncertainties over some structural assumptions that are not reflected in the PSA.

**Model validation**

The decision tree model was validated by checking its structure, calculations and data inputs for technical correctness. The model structure was reviewed by clinical experts for appropriateness for the disease and diagnosis. The model was checked for internal consistency by a second health economist. The robustness of the model to changes in input values was tested using sensitivity analyses to ensure that any changes to the input values produced changes to the results of the expected direction and magnitude.

The prediction of correct surveillance intervals was compared between the estimates from the model and those in the published literature. Three studies of NBI9,68,69 that reported both accuracy of diagnosing individual diminutive polyps and accuracy of assignment of patients to surveillance interval using data from diminutive polyps only were identified by our systematic review of diagnostic studies. In Chandran and colleagues,68 the diagnostic accuracy was 91.2% whilst the surveillance interval was correctly determined in 98% of patients. In Gupta and colleagues (2012),69 the diagnostic accuracy was 84.8%, whilst prediction of surveillance interval was accurate in 86.1% to 94.1% of patients if only diminutive polyps were considered. In Paggi and colleagues (2012),9 diagnostic accuracy for diminutive polyps was 84.0% whilst correct surveillance intervals were applied 85.3% of the time. None of the i-scan or FICE studies identified by our systematic review reported of the accuracy of assignment of patients to a surveillance interval based on diminutive polyps only. The model predicted correct surveillance intervals in 93% to 98% of patients using the virtual chromoendoscopy technologies.

The majority of the estimates of correct surveillance interval prediction identified by our systematic review of diagnostic studies (Section ‎4.1.3) were based on using virtual chromoendoscopy characterisations for polyps <5mm in size (or in some studies <10mm in size) combined with histopathological assessment of all other polyps (14/17 studies). In these 14 studies3,5,6,10-14,71,77,79,82-84 the estimates of correct surveillance interval prediction range between 79.9% and 100% across all virtual chromoendoscopy technologies; only in three of the NBI studies6,12,77 did some agreements fall below 90.0% . The surveillance interval prediction from our model is broadly consistent with the systematic review findings.

Model parameters

The following sub-sections report parameters included in the model. The model parameters include polyp and adenoma demographics, diagnostic test accuracy, adverse event rates, health sector costs (such as cost of colonoscopy), HRQoL and long-term epidemiology (such as disease progression). The costs and adverse event parameters have been based upon those previously used in the SBCS model121 and updated, where necessary.

* + - 1. Prevalence of polyps and adenomas

The prevalence of patients presenting with different numbers of polyps and adenomas at colonoscopy were estimated from the literature for three populations: the screening population (base case), and the surveillance and symptomatic populations (used in scenario analyses).

**Screening population**

We searched for studies that described the distribution of polyps in patients in a bowel screening population. We identified one study by Raju and colleagues128 who reported data for the distribution of polyps and adenomas per patient. We analysed the distribution of polyps and adenomas to derive the average number of polyps and adenomas for low risk (LR), intermediate risk (IR) and high risk (HR) patients and the frequency of patients in each risk category, assuming all polyps are diminutive.

Raju and colleagues128 is a retrospective analysis of data from a colon cancer screening programme in the USA. Three hundred and forty three patients underwent colonoscopy between 2009 and 2011. In the study, 46 patients had no polyps, and there were 882 polyps in the remaining 297 patients (2.97 polyps per patient). Of the patients that had polyps, there were 206 patients who had a total of 422 adenomas, i.e. 1.4 adenomas per patient with a polyp, or 2.04 per patient with an adenoma. Thirty percent of patients who had polyps had no adenomas.

We used a graphical data extraction programme (XY Scan)129 to extract the data from Raju and colleagues. This extraction resulted in a slight overestimation of the number of adenomas (426 instead of the reported 422) and the number of patients with adenomas (207 instead of 206) in order to keep polyp numbers correct at 882.

In order to calculate the number of polyps per patient in each risk category, we assumed that the overall prevalence of patients with adenomas was evenly distributed across the risk categories, where people had adenomas. The risk stratification was defined according to the current BSG guidelines41 where people with 1-2 adenomas are low risk, those with 3-4 adenomas are intermediate risk and those with five or more adenomas are high risk. First, we calculated the proportion of patients with the number of adenomas that corresponded with the risk classification and then we calculated a weighted average of the number of polyps and adenomas in these patients. The derivation of the polyp demographics are shown in more detail in Appendix 10. Polyp demographics are shown in Table 37.

Table Prevalence of polyps and adenomas by risk classification for bowel cancer screening patients at colonoscopy

|  |  |  |
| --- | --- | --- |
| **Polyp demographics in patients with at least one polyp** | **Value** | **Source** |
| Prevalence of patients with at least one adenoma | 0.698 | Raju et al.128 |
| Prevalence of patients with no adenomas | 0.302 | Raju et al.128 |
| Prevalence of patients with low risk | 0.535 | Raju et al.128 |
| Prevalence of patients with intermediate risk adenoma | 0.107 | Raju et al.128 |
| Prevalence of patients with high risk | 0.056 | Raju et al.128 |
| Average number of polyps | 2.97 | Raju et al.128 |
| Number of polyps, low risk patients | 2 | Raju et al.128 |
| Number of polyps, intermediate risk patients | 4.78 | Raju et al.128 |
| Number of polyps, high risk patients | 8.47 | Raju et al.128 |
| Number of adenomas, low risk patients | 1.4 | Raju et al.128 |
| Number of adenomas, intermediate risk patients | 3.34 | Raju et al.128 |
| Number of adenomas, high risk patients | 5.91 | Raju et al.128 |

**Surveillance population**

We were unable to identify any studies that reported the distribution of adenomas in a surveillance population, whereby all patients after colonoscopy had been followed-up for the appropriate surveillance interval as defined by their risk classification. We found several studies that reported the distribution of adenomas at follow-up surveillance for specific subgroups. For example, Lee and colleagues130 reported the outcome of 12 month surveillance colonoscopy in high risk patients (n=1760) in the NHS Bowel Cancer Screening Programme. Martinez and colleagues131 reported a pooled analysis of eight prospective studies comprising 9167 people with previously resected colorectal adenomas during a median follow-up of four years. We found several other studies that reported the distribution of adenomas at various follow-up intervals for patients with more than one adenoma resected.132,133 In the absence of data that fit our population group, we used these studies, together with an assumption to calculate the distribution of adenomas in this population.

The proportion of patients with no adenomas at follow-up surveillance was similar for Lee and colleagues130 (49.2%) and Martinez and colleagues131(53.3%). We chose the estimate from Martinez and colleagues131 as it was the larger study and not only for high risk patients. We stratified those patients that had low risk, intermediate or high risk adenomas in the same proportion as for the screening population (Table 37). The resulting distribution of adenomas for the surveillance population is shown in Table 38.

Table Proportion of patients by risk category for surveillance and symptomatic populations

|  |  |  |
| --- | --- | --- |
| **Distribution of patients** | **Surveillance population** | **Symptomatic population** |
| No adenoma | 0.533 | 0.782 |
| Low risk | 0.358 | 0.125 |
| Intermediate risk | 0.072 | 0.061 |
| High risk | 0.037 | 0.032 |

**Symptomatic population**

We identified one relevant study by Mcdonald and colleagues134 that described the proportion of people who had adenomas in a group of consecutive patients referred from primary care for colonoscopic examination in the NHS. Patients were referred for symptoms including rectal bleeding, change in bowel habits and abdominal pain. No patients were included if they had been referred as a result of the Bowel Cancer Screening Programme. The distribution of adenomas for the symptomatic population is shown in Table 38.

The study also included a small number of patients with irritable bowel syndrome and we have excluded these from our calculation of the distribution of adenomas in the symptomatic population. The study reports the number of people who have no adenomas, low risk adenomas and high risk adenomas. The high risk adenoma group was split between intermediate risk and high risk in the same proportion as for the screening population (Table 38).

* + - 1. Diagnostic accuracy

The sensitivity and specificity of histopathology and the virtual chromoendoscopy technologies are taken from the meta-analyses conducted in this report, as described in Section ‎4. We have assumed that histopathology provides an accurate diagnosis of all polyps (i.e. 100% sensitivity and specificity). The diagnostic accuracy parameters are shown in Table 39 andare for high confidence characterisations of polyps in the whole colon. The proportion of polyps assessed with low confidence is derived from those NBI studies in our systematic review that reported these data and is assumed to be the same for FICE and i-scan.

Scenario analyses were conducted for alternative diagnostic accuracy estimates derived from the systematic review and meta-analysis in section ‎5.5.2, as follows:

* Sensitivity and specificity for polyps characterised with high confidence in the rectosigmoid colon
* Sensitivity and specificity for polyps characterised with any confidence level in the rectosigmoid colon
* Sensitivity and specificity for polyps characterised with any confidence level in the whole colon
* Sensitivity and specificity for a pooled VCE analysis
* Sensitivity and specificity for endoscopists experienced in the use of NBI

Table Sensitivity and specificity for histopathology, NBI, i-scan and FICE

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Value** | **Lower 95% CI** | **Upper 95% CI** | **Source** |
| Histopathology sensitivity | 1 |  |  | Assumption |
| Histopathology specificity | 1 |  |  | Assumption |
| NBI sensitivity | 0.910 | 0.855 | 0.945 | Meta-analysis |
| NBI specificity | 0.819 | 0.760 | 0.866 | Meta-analysis |
| FICE sensitivity | 0.814 \* | 0.732 | 0.875 | Meta-analysis |
| FICE specificity | 0.850 \* | 0.786 | 0.898 | Meta-analysis |
| i-scan sensitivity | 0.962 | 0.917 | 0.983 | Meta-analysis |
| i-scan specificity | 0.906 | 0.842 | 0.946 | Meta-analysis |
| Proportion low confidence | 0.214 | 0.21 | 0.22 | NBI studies that reported these data in our review |

\* As there were no data available for sensitivity and specificity for FICE characterisations with high confidence, we have used data from our meta-analysis of FICE with any level of confidence

* + - 1. Adverse effects

There are small risks attached to polypectomy such as bowel perforation and bleeding which may lead to hospitalisation and, for those patients who experience perforation, a small risk of death. The probabilities of these adverse effects were taken from the published sources used in the SBCS model and are shown in Table 40.

Table Probabilities of adverse events for perforation and bleeding for patients receiving polypectomy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Value** | **Lower 95% CI** | **Upper 95% CI** | **Source** |
| Probability of perforation with polypectomy | 0.003 | 0 | 0.01 | Whyte et al.121 |
| Probability of death, for patients with perforation during polypectomy | 0.052 | 0.01 | 0.11 | Gatto et al.135 |
| Probability of hospitalisation for bleeding with polypectomy | 0.003 | 0 | 0.01 | Atkin et al.136 |

* + - 1. Estimation of costs

Costs were included for colonoscopy, polypectomy, adverse events and histopathology. The unit costs were taken from the NHS Reference costs for 2014/15.122 A summary of the unit costs is shown in Table 41.

Table Unit costs for colonoscopy and treating adverse events

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Value** | **Lower 95% CI** | **Upper 95%CI** | **Source** |
| Cost of colonoscopy without polypectomy | £518.36 | £340.89 | £695.83 | HRG 2014-15 FZ51Z, Day case |
| Cost of colonoscopy with polypectomy | £600.16 | £406.24 | £794.08 | HRG 2014-15  FZ52Z, Day case |
| Cost of treating bowel perforation (major surgery) | £2,152.77 | £902.21 | £3,403.33 | HRG 2014-15 FZ24E-J Weighted average, non-elective long stay |
| Cost of admittance for bleeding (overnight stay on medical ward) | £475.54 | £327.69 | £623.39 | HRG 2014-15 FZ38G-P Weighted average, non-elective short stay |
| Pathology cost per polyp examination | £28.82 | £6.78 | £50.86 | HRG 2014-15 DAPS02 |

**System costs**

The equipment and maintenance costs for virtual chromoendoscopy technologies are shown in Appendix 11. These costs are not included in the base case analysis for virtual chromoendoscopy versus histopathology as all equipment and maintenance costs are included within the National Reference Costs for colonoscopy and polypectomy (Table 41). There are differences in the costs between the virtual chromoendoscopy technologies and these are explored in a scenario analysis (section ‎5.5.2).

**Colorectal cancer treatment costs**

The SBCS model includes colorectal cancer treatment costs by patient age and Dukes’ colorectal cancer staging score. These costs were taken from the study by Pilgrim and colleagues137 and have been inflated to 2015 prices using The Hospital & Community Health Services (HCHS) index123 (Table 42).

Table Updates to parameter values in the SBCS model: Bowel cancer screening and colorectal cancer treatment costs (inflated to 2015)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Dukes’ colorectal cancer stage at diagnosis** | | | |
| Age at diagnosis | A | B | C | D |
| 40-49 | £8,871 | £8,858 | £14,683 | £11,862 |
| 50-59 | £5,789 | £7,110 | £9,821 | £8,557 |
| 60-69 | £4,686 | £5,423 | £7,357 | £6,596 |
| 70-79 | £3,220 | £3,500 | £4,546 | £4,423 |
| 80-100 | £1,398 | £1,567 | £1,581 | £818 |

* + - 1. Training costs

As discussed earlier (Section ‎1.2.6) in order for endoscopists to accurately use virtual chromoendoscopy, they will need to receive training. This may entail training programmes in the form of video packages and/or supervision from endoscopists experienced in using virtual chromoendoscopy. Several studies have evaluated training packages that were developed to train endoscopists in the use of NBI.73,90,138,139

For example, Ignjatovic and colleagues138 conducted a prospective education study on a computer-based training module on 21 individuals (novices, trainees, and experienced gastroenterologists) with varying colonoscopy experience in the UK. There was significant improvement in the accuracy in characterisation of polyps after the training. Ignjatovic and colleagues138 commented that although the NBI learning curve is thought to be relatively short, with an improvement in diagnostic accuracy after as few as 44 polyps, it is not clear how expertise is best transferred to community gastroenterologists and to trainees. McGill and colleagues73 showed that the performance of endoscopists could be sustained over time by repeating the training module at the mid-point of the study. Meads and colleagues139 suggest that ongoing training and assessment is necessary to sustain performance.

We assumed the number of days training would be two days per year per endoscopist in common with the NBI study by Solon and colleagues.116 Using a daily rate for endoscopists of £1104 from PSSRU,123 and assuming each endoscopist completes 150 endoscopies per year gives a training cost per patient of £14.72.

* + - 1. Health-related quality of life

The SBCS model121 used a study by Ara and Brazier140 that reported utility values. Ara and Brazier pooled the data from four Health Surveys for England in order to compare self-reported health status and quality of life response for subjects with or without a specified list of health conditions. The mean EQ-5D score for respondents was 0.697, while those without cancer the mean EQ-5D score was 0.798. The mean age for respondents for this health state was 60.9 years.

We conducted a targeted search for other studies reporting the HRQoL for patients with colorectal cancer. The searches sought to identify studies reporting EQ-5D that described the HRQoL in general of patients with colorectal cancer, rather than a specific stage of colorectal cancer, such as metastatic cancer. The searches identified three potentially relevant studies summarized in Table 43. One study was from the UK, one study was from the USA141 and one from Finland.142

Table Summary of HRQoL studies identifed

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Year** | **Country** | **Study type** | **Population** | **EQ-5D values** |
| Djalalov et al.141 | 2014 | USA | Systematic review and meta-analysis | 26 studies that reported utility weights for CRC health states. 6543 respondents (mean age 62 years) | 0.76 |
| Farkkila et al.142 | 2013 | Finland | Cross-sectional study | 508 Finnish CRC patients  (mean age 68 years )  Patients were divided into five groups: primary treatment, rehabilitation, remission, metastatic disease and palliative care. | Remission: 0.85; All patients 0.813. |
| Downing et al.143 | 2015 | UK | Population-level study | All individuals diagnosed with CRC in England in 2010 and 2011 who were alive 12 to 36 months after diagnosis were sent a questionnaire. 21,802 of 34,467 patients responded. | Mean EQ-5D values not reported. |

CRC - colorectal cancer

Djalalov and colleagues141 performed a systematic review of utility weights for colorectal cancer. They identified 26 studies providing unique utilities for colorectal cancer health states elicited from 6546 respondents. They included utility assessments including the EQ-5D, HUI3 and time-trade off. The colorectal cancer utility data were analysed using linear mixed-effects models for different variables including colorectal cancer type, stage, and utility measure. They calculated the mean EQ-5D score of the population of people with colorectal cancer to be 0.76. It is unclear if this estimate captures the overall HRQoL for patients with colorectal cancer as there was a greater number of studies included with more severe disease in the meta-analysis, and the overall mean utility score reflects this.

Farkkila and colleagues142 provide utility values for patients with colorectal cancer in Finland. In this study, patients diagnosed with colorectal cancer received a questionnaire by mail. A total of 508 patients assessed their HRQoL using generic 15D and EQ-5D (with the UK tariff). Patients were divided into five groups: primary treatment, rehabilitation, remission, metastatic disease and palliative care. The patients’ HRQoL was compared to population reference values. The study reported an EQ-5D utility value of 0.813 for all patients with colorectal cancer and 0.85 for patients in cancer remission. The utility values were higher for patients in remission than the standardized general population (non-significant difference). For the purposes of our analysis, we assumed that patients in remission have similar utility to the general population, and therefore the mean decrement for colorectal cancer patients is 0.037.

Downing and colleagues143 sent a questionnaire to all individuals diagnosed with colorectal cancer in England in 2010 and 2011, who were alive 12 to 36 months after diagnosis and 21,802 patients responded. The questionnaire included questions related to treatment, disease status and HRQoL (EuroQoL). However, Downing and colleagues143 did not provide mean EQ-5D values.

For our base case analysis, we used HRQoL values from Ara and Brazier,140 for consistency with the SBCS model. We explored alternative quality of life values from Farkkila and colleagues142 in a scenario analysis.

* + - 1. Disutility

Disutility values were sought for patients who experience adverse events during polypectomy such as bowel perforation or bleeding. However, we were not able to identify values for disutilities for these events from the literature. As an alternative we estimated values for disutility for bleeding by assuming they would be similar to a major gastrointestinal bleed and used the value from Dorian and colleagues144 of 0.1511 for two weeks, i.e. a total QALY loss of 0.006. Values for perforation were assumed to be the same as for stomach ulcer/abdominal hernia/rupture taken from Ara and Brazier.140 The disutility value was 0.118 for one month, i.e. total QALY loss of 0.010.

* + - 1. Epidemiology of adenoma and cancer progression

Transition probabilities in the SBCS natural history model (progression between the adenoma states, pre-clinical CRC stages and from pre-clinical to clinical CRC stages) and screening test characteristics were estimated using a calibration approach. These parameters are not observable, so they were inferred based on available data on CRC incidence by age and stage in the absence of screening, and from CRC screening datasets. Results are presented in Whyte et al 2012.121

The SBCS model uses cancer recurrence rates for people from the NHS bowel cancer screening programme with high risk adenomas and data from a study by Martinez and colleagues131 for people with low risk adenomas; see Table 44. The proportion of people in the high risk surveillance category who have had a polypectomy requiring annual surveillance is 0.29. Full details of the data and assumptions used are available in Whyte and colleagues.121

Table Adenoma recurrence probabilities used in the SBCS model

|  |  |  |
| --- | --- | --- |
| **Description** | **Probability of transition to** | **Value** |
| LR adenoma, all adenomas resected | LR adenomas health state | 0.100 |
| LR adenoma, all adenomas resected | LR adenomas health state | 0.040 |
| LR adenoma, all adenomas resected | CRC health state | a |
| HR adenoma (IR), all adenomas resected | LR adenomas health state | 0.163 |
| HR adenoma (IR), all adenomas resected | LR adenomas health state | 0.091 |
| HR adenoma (IR), all adenomas resected | CRC health state | a |
| HR adenoma (HR), all adenomas resected | LR adenomas health state | 0.188 |
| HR adenoma (HR), all adenomas resected | LR adenomas health state | 0.568 |
| HR adenoma (HR), all adenomas resected | CRC health state | a |
| \*assumed to be the probability of transitioning from normal epithelium to Dukes’ A | | |

CRC - colorectal cancer

To ensure consistency between the model parameters, it is important that the post-polypectomy transition probabilities used align with the other natural history transition probabilities in the model. It was assumed that persons who are undergoing surveillance post-polypectomy are at higher risk of developing adenomas than persons with a normal epithelium, and that polypectomy reduces the risk of developing CRC. Hence restrictions were placed on the post-polypectomy transition probabilities as described in Table 45.

Table SBCS restrictions on transition probabilities post-polypectomy



* + - 1. Long-term estimates of costs and QALYs

Table 46 presents the results of the SBCS analyses, showing expected discounted costs and QALYs for patients at each of the diagnostic endpoints from the decision tree model (as listed in Table 34). Estimates are for one person aged 65 years in each diagnostic category, from the end of colonoscopy after a positive FOBT result with removel of polyps if indicated, and then modelled over a lifetime horizon. The costs presented here do not include costs for the initial colonoscopy, polypectomy, histopathology or adverse events, which are modelled in the decision tree. They do include costs for subsequent follow up, including routine screening and surveillance , and for treatment of any incident cancers. Similarly, the QALY estimates do not include effects of any adverse events associated with the initial colonoscopy and polypectomies, but they do include adverse effects associated with subsequent rounds of screening or surveillance, and with incident cancers.

Table Expected lifetime costs and QALYs for 1 person aged 65 undergoing colonoscopy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Initial risk (adenomas)** | **Patient outcome** | **Adenomas missed** | **Hyperplastic polyps resected** | **Surveillance interval** | **Costs, £,** | **QALYsa** | **QALYsb** |
| LR (0) | CD | None | None | Invited to screening | 109 | 11.26653 | 11.27254 |
| HPRC | None | One or more | Invited to screening | 109 | 11.26653 | 11.27254 |
| LR (1-2) | CD | None | None | Invited to screening | 109 | 11.26653 | 11.27254 |
| HPRC | None | One or more | Invited to screening | 109 | 11.26653 | 11.27254 |
| HPRI | None | One or more | 3 year surveillance | 1075 | 11.29947 | 11.30355 |
| MAI\* | One or more | None | Invited to screening | 250 | 11.26399 | 11.27027 |
| MAC\* | One or more | None | Invited to screening | 250 | 11.26399 | 11.27027 |
| HPRMA\* | One or more | One or more | Invited to screening | 250 | 11.26399 | 11.27027 |
| IR (3-4) | CD | None | None | 3 year surveillance | 1097 | 11.29934 | 11.30341 |
| HPRC | None | One or more | 3 year surveillance | 1097 | 11.29934 | 11.30341 |
| HPRI | None | One or more | Annual surveillance | 1577 | 11.32057 | 11.30659 |
| MAI \* | One or more | None | Invited to screening | 250 | 11.26399 | 11.27027 |
| MAC | One or more | None | 3 year surveillance | 1161 | 11.29891 | 11.30291 |
| HPRMA | One or more | One or more | 3 year surveillance | 1161 | 11.29891 | 11.30291 |
| HR (5+) | CD | None | None | Annual surveillance | 1584 | 11.30252 | 11.30654 |
| HPRC | None | One or more | Annual surveillance | 1584 | 11.30252 | 11.30654 |
| HPRI | None | One or more | Annual surveillance | 1584 | 11.30252 | 11.30654 |
| MAI | One or more | None | 3 year surveillance | 1161 | 11.29891 | 11.30291 |
| MAC | One or more | None | Annual surveillance | 1681 | 11.30152 | 11.30553 |
| HPR\_MA | One or more | One or more | Annual surveillance | 1681 | 11.30152 | 11.30553 |
| a QALYs using quality of life estimates from Ara and Brazier140  b QALYs using quality of life estimates from Farkkila et al.142  \* Results for patients with missed adenomas adjusted to ensure that costs and QALYs are less favourable than if all adenomas had been removed with the same follow up. | | | | | | | |

Results from the SBCS model were counter-intuitive for patients with one or more adenomas missed and left in situ and routine screening follow up. Estimated QALYs for this group (11.26730) were higher than for patients with all adenomas resected and the same follow up interval (11.26653 for LR). Similarly, long-term cost estimates for patients with routine screening were lower if adenomas were missed (£98) than if all adenomas had been successfully identified and removed (£109). This small inconsistency appears to result from the assumptions about direct (de novo) incidence of cancers from the ‘adenomas removed’ and ‘adenomas in situ’ health states (see Figure 34). In the LR group, if all ademonas are removed, the risk of progression to cancer through this direct route compensates for the reduced risk of cancer via the adenoma-carcinoma pathway. To compensate for this effect we adjusted the estimated QALYs and costs for patients with adenomas left in situ and routine screening. We calculated the QALY loss of having adenomas left in situ compared with having all adenomas removed for the HR group with routine screening and similarly with 3-yearly surveillance. Then we calculated the ratio between the 3-year surveillance QALY loss and the routine screening QALY loss. This ratio was then assumed to be the same for the LR group. The same method was used to adjust the cost estimate for LR patients with adenomas lef t in situ and routine screening.

* 1. Results of the independent economic analysis
     1. Base case cost-effectiveness results

The base case analysis patients in the model are those undergoing bowel cancer screening with a starting age of 65 years. The colonoscopy costs are derived from NHS Reference Costs and include the cost of the colonoscopy equipment and its maintenance in the base-case, with all system costs (endoscope, system, and maintenance) identical across interventions. A sensitivity analysis is conducted using costs system, scope and maintenance costs from each manufacturer in section ‎5.5.2.2.

Table 47 reports the clinical outputs produced by the decision tree model. In the histopathology strategy, all polyps are resected, whilst between 58% and 63% of polyps are resected for FICE and NBI respectively. Virtual chromoendoscopy reduces the number of hyperplastic polyps resected from 1.53 in the histopathology alone strategy to between 0.06 (i-scan) and 0.14 (FICE) but leaves some adenomas in situ (between 0.04 for i-scan and 0.21 for FICE). Virtual chromoendoscopy reduces adverse events due to bleeding and perforations, and deaths from perforations by roughly a third. The incidence of colorectal cancer is about 3% for all technologies (Appendix 12). The correct surveillance interval estimated in the model varies for the virtual chromoendoscopy technologies between 94% (FICE) and 97% (i-scan).

Table Clinical outcomes from the decision tree, for a hypothetical patient receiving colonoscopy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Histopathology** | **NBI** | **FICE** | **i-scan** |
| Polypectomy | 100.00% | 63.38% | 58.42% | 61.84% |
| Polyps resected | 2.97 | 1.47 | 1.37 | 1.45 |
| Hyperplastic polyps resected | 1.53 | 0.13 | 0.14 | 0.06 |
| Hyperplastic polyps left in situ | 0 | 1.40 | 1.39 | 1.48 |
| Adenomas resected | 1.44 | 1.33 | 1.22 | 1.39 |
| Adenomas left in situ | 0 | 0.10 | 0.21 | 0.04 |
| Bleeding events | 0.003 | 0.00190 | 0.00175 | 0.00186 |
| Perforations | 0.003 | 0.00190 | 0.00175 | 0.00186 |
| Perforation deaths | 0.000156 | 0.000099 | 0.000091 | 0.000096 |
| Adenomas left in situ (%) | 0.00% | 7.13% | 14.70% | 3.04% |
| Hyperplastic polyps resected (%) | 100.00% | 8.68% | 9.44% | 3.68% |
| Correct Surveillance Interval | 100% | 94.7% | 93.8% | 97.4% |
| Incidence of colorectal cancer | 3.025% | 3.020% | 3.045% | 3.021% |

The incremental results of the base case deterministic analysis with the long-term model are presented in Table 48. Where an intervention is dominated (more costly and less effective), the calculation of incremental costs for the next least costly intervention is compared to the next non-dominated intervention. Pairwise comparisons to histopathology are also presented for NBI, FICE and i-scan, respectively, for full incremental costs, QALYs, and ICERs.

Table Cost-effectiveness results of the lifetime economic model

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Costs** | **Incremental**  **Costs** | **QALYs** | **Incremental**  **QALY** | **ICER (£ per QALY)** |
| **Full incremental results** | | | | | |
| Histopathology | £988.95 | -- | 11.2703 | -- | Dominated |
| FICE | £901.25 | -£87.70 | 11.2701 | -0.0001 |  |
| i-scan | £909.74 | £8.49 | 11.2709 | 0.0008 | £10,465.74 |
| NBI | £915.85 | £6.11 | 11.2708 | -0.0001 | Dominated |
| **Pairwise comparisons** | | | | | |
| Histopathology | £988.95 |  | 11.2703 |  |  |
| NBI | £915.85 | -£73.10 | 11.2708 | 0.0005 | Dominates |
| Histopathology | £988.95 |  | 11.2703 |  |  |
| FICE | £901.25 | -£87.70 | 11.2701 | -0.0001 | £671,383 \* |
| Histopathology | £988.95 |  | 11.2703 |  |  |
| i-scan | £909.74 | -£79.21 | 11.2709 | 0.0007 | Dominates |

\* Incremental cost saving per QALY lost.

In pairwise comparisons, NBI and i-scan and FICE are cost-saving compared to histopathology. The QALYs for virtual chromoendoscopy and histopathology are similar with very small differences between the technologies. Technically, NBI and i-scan dominate histopathology, i.e. they are cheaper and more effective. FICE is more cost effective than histopathology, as the ICER for histopathology vs. FICE is greater than £30,000 per QALY. The difference between histopathology and i-scan, the most effective intervention, was 0.25 Quality Adjusted Days per individual. The differences in costs between the virtual chromoendoscopy technologies were less than £15 over a patient lifetime. I-scan is £79 less costly than histopathology and produces 0.0007 more QALYs. Virtual chromoendoscopy technologies have a cost saving of about £50 per polyp resection avoided compared to histopathology.

Table 49 shows the costs and QALYs for the intial colonoscopy and for the long-term component for each risk group for NBI vs. histopathology. Most of the cost savings occur for the initial colonoscopy. For the low risk group, the long-term costs are higher for NBI, due to the small proportion of patients who are assigned to a more frequent surveillance interval. Most of the QALY gains for NBI are from the reduction in deaths from perforation. There are QALY gains for NBI for patients assigned to more frequent surveillance interval, particularly for patients with low risk, and QALY losses for patients with adenomas left in situ and assigned to less frequent surveillance interval.

Table Summary of the costs and QALYs for the intial colonoscopy and the long-term components

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Costs, £** | | | **QALYs** | | |
|  | Histopathology | NBI | Difference | Histopathology | NBI | Difference |
| Initial colonoscopy | £691.68 | £607.46 | 84.22 | -0.00005 | -0.00003 | -0.00002 |
| 0 adenomas | £32.88 | £32.88 | 0.00 | 3.3986 | 3.3990 | -0.0003 |
| LR adenoma | £58.34 | £83.08 | -24.74 | 6.0298 | 6.0305 | -0.0007 |
| IR adenoma | £117.42 | £108.36 | 9.06 | 1.2095 | 1.2090 | 0.0005 |
| HR adenoma | £88.63 | £84.07 | 4.56 | 0.6324 | 0.6324 | 0.0000 |
| Total | £988.95 | £915.85 | 73.10 | 11.2703 | 11.2708 | -0.0005 |

* + 1. Sensitivity analyses
       1. One-way deterministic sensitivity analyses

Parameters were varied across a range of lower and upper values. The parameters that were varied in one-way sensitivity analyses are reported in Table 50 and Table 51. Most of the one-way sensitivity analyses use 95% confidence intervals from data identified during our systematic review and targeted parameter searches. However, some data were taken from different ranges, for example to show the variation between studies for these data. The prevalence of adenomas were varied across the possible range for each risk classification.

Table Parameter values used in one-way sensitivity analyses

| **Parameter** | **Mean** | **Lower** | **Upper** | **Range definition** |
| --- | --- | --- | --- | --- |
| NBI Sensitivity | 0.910 | 0.855 | 0.945 | 95% CI |
| NBI Specificity | 0.819 | 0.760 | 0.866 | 95% CI |
| FICE Sensitivity | 0.814 | 0.732 | 0.875 | 95% CI |
| FICE Specificity | 0.850 | 0.786 | 0.898 | 95% CI |
| i-scan Sensitivity | 0.962 | 0.917 | 0.983 | 95% CI |
| i-scan Specificity | 0.906 | 0.842 | 0.946 | 95% CI |
| Proportion Low Confidence Assessments | 0.210 | 0.105 | 0.315 | Assumed range |
| Prevalence of adenomas in patients with polyps | 0.698 | 0.600 | 0.800 | Assumed range |
| Average adenomas in patients that have low risk adenomas | 1.395 | 1 | 2 | Assumed range |
| Average adenomas in patients that have intermediate risk adenomas | 3.341 | 3 | 4 | Assumed range |
| Average adenomas in patients that have high risk adenomas | 5.913 | 5 | 9 | Assumed range |
| Probability of perforation with polypectomy | 0.003 | 0.000 | 0.010 | 95% CI |
| Probability of perforation death | 0.052 | 0.010 | 0.110 | 95% CI |
| Probability of hospitalisation for bleeding | 0.003 | 0.000 | 0.010 | 95% CI |
| Cost of colonoscopy (without polypectomy) | £518.36 | £340.89 | £695.83 | 95% CI |
| Cost of colonoscopy (with polypectomy) | £600.16 | £406.24 | £794.08 | 95% CI |
| Cost of treating bowel perforation (major surgery) | £2,152.77 | £902.21 | £3,403.33 | 95% CI |
| Cost of admittance for bleeding (overnight stay on medical ward) | £475.54 | £327.69 | £623.39 | 95% CI |
| Pathology cost | £28.82 | £6.78 | £50.86 | 95% CI |
| Training cost | £14.72 | £10.30 | £19.14 | 95% CI = +/- 30% of mean |

Data were not available for the uncertainty around the long-term outcomes. We included one-way sensitivity analyses for these outcomes but used arbitrary ranges. We included the long-term outcomes for patients with incorrect diagnoses, i.e. false negatives and false positives in each risk category, for both costs and QALYs. The ranges used were calculated by adding or subtracting half the difference between a correct diagnosis and the false diagnosis in either costs or QALYs. The ranges used are reported in Table 51.

Table Parameter values used in one-way sensitivity analyses for long-term outcomes for patients with incorrect diagnoses

|  | **Mean** | **Lower CI** | **Upper CI** | **Assumption** |
| --- | --- | --- | --- | --- |
| **Health State Costs** | | | | |
| LR Hyperplastic polyps resected | £1,075 | £592 | £1,558 | CI = 50% of difference between HPR and CD |
| LR Missed adenoma | £250 | £180 | £321 | CI = 50% of difference between MA and CD |
| IR Hyperplastic polyps resected | £1,577 | £1,337 | £1,817 | CI = 50% of difference between HPR and CD |
| IR Missed adenoma | £250 | £0 | £674 | CI = 50% of difference between MA and CD |
| HR Hyperplastic polyps resected | £1,584 | £1,584 | £1,584 | CI = 50% of difference between HPR and CD |
| HR Missed adenoma | £1,161 | £950 | £1,373 | CI = 50% of difference between MA and CD |
| **Health State QALY** | | | | |
| LR Hyperplastic polyps resected | 11.2830 | 11.2830 | 11.3159 | CI = 50% of difference between HPR and CD |
| LR Missed adenoma | 11.2627 | 11.2627 | 11.2653 | CI = 50% of difference between MA and CD |
| IR Hyperplastic polyps resected | 11.3010 | 11.3010 | 11.3042 | CI = 50% of difference between HPR and CD |
| IR Missed adenoma | 11.2463 | 11.2463 | 11.2817 | CI = 50% of difference between MA and CD |
| HR Hyperplastic polyps resected | 11.3025 | 11.3025 | 11.3025 | CI = 50% of difference between HPR and CD |
| HR Missed adenoma | 11.2971 | 11.2971 | 11.3007 | CI = 50% of difference between MA and CD |
| LR low risk (1-2 adenomas), IR intermediate risk (3-4 adenomas), HR high risk (≥5 adenomas), HPR hyperplastic polyp resected, MA missed adenoma, CD correct diagnosis | | | | |

The results of the one-way sensitivity analyses for each virtual chromoendoscopy technology: NBI, FICE, and i-scan (Figure 35 - Figure 37) are presented as pairwise comparisons to histopathology.

For each virtual chromoendoscopy technology, there were 25 parameters evaluated and the 11 most influential parameters on the model results are presented in the corresponding tables. The results show the changes in incremental net monetary benefits, rather than the change in ICERs. As the ICERs are negative, these values are more difficult to interpret.

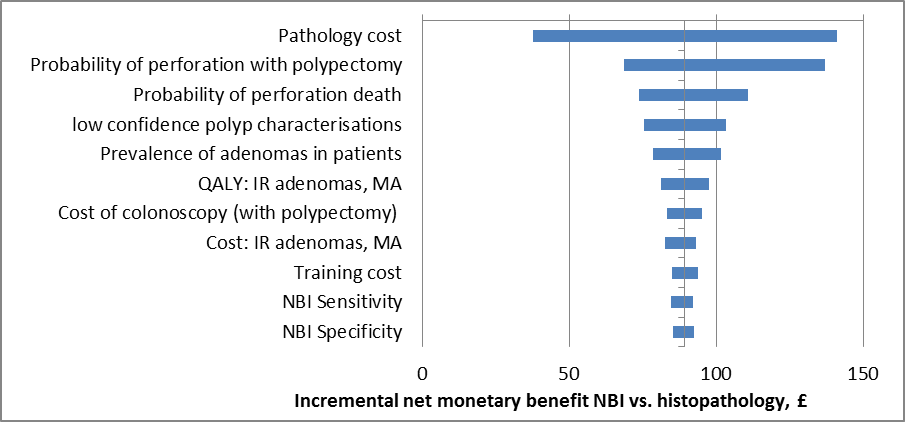


Figure Tornado plot of one-way sensitivity analyses for NBI

For NBI compared to histopatholgy, NBI remained the dominant strategy for all sensitivity analyses. Figure 35 shows that, for NBI compared to histopathology, the most influential parameters on the model results are the pathology cost, the probability of perforation with polypectomy and the proportion of patients who die from perforation, and the long-term QALY estimate for intermediate patients with a missed adenoma.

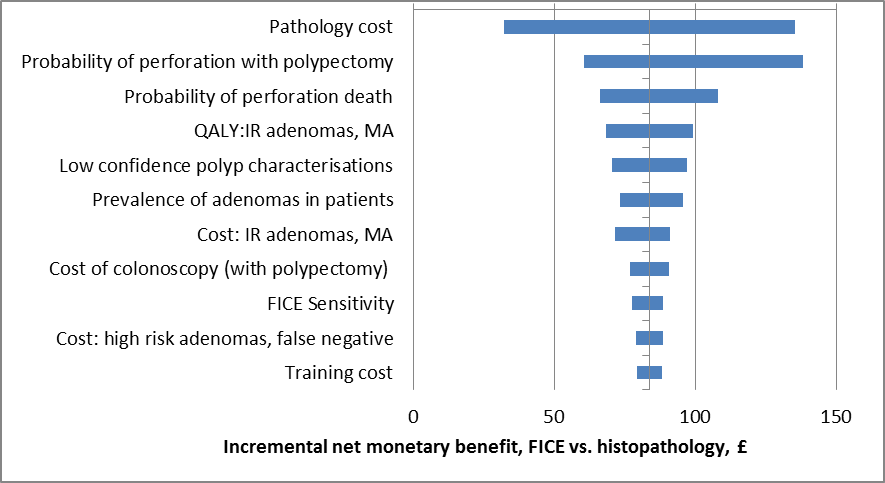


Figure Tornado plot of one-way sensitivity analyses for FICE

Figure 36 shows that, for histopathology compared to FICE, the most influential parameters on the model results are the pathology cost, the probability of perforation with polypectomy and the proportion of patients who die from perforation, and the proportion of low confidence characterisations made at low confidence. FICE remained more cost effective than histopathology for all sensitivity analyses.

Figure Tornado plot of one-way sensitivity analyses for i-scan

The most influential parameters on the model results for one-way analyses comparing i-scan to histopathology are the pathology cost, the probability of perforation with polypectomy, and the proportion of polyp characterisations made at low confidence.

* + - 1. Scenario analyses

In this section, twelve scenario analyses are explored. The descriptions of the scenario analyses are provided in Table 52. Further description of the components of each analysis follow the table.

Table Description of the scenario analyses

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Analysis** | **Diagnostic Accuracy (Part of colon – confidence in characterisation)1** | **Other parameters changed** |
| 0 | Base case | Whole colon – high |  |
| 1 | Surveillance patients | Whole colon – high | Starting risk distributions changed |
| 2 | Symptomatic patients | Whole colon – high | Starting risk distributions changed |
| 3 | DISCARD71 | Rectosigmoid – high | Only polyps in rectosigmoid colon may be left in situ |
| 4 | DISCARD71 | Whole colon – high | Only polyps in rectosigmoid colon may be left in situ |
| 5 | DISCARD71 | Whole colon – any | Only polyps in rectosigmoid colon may be left in situ |
| 6 | VC Strategy | Whole colon – any |  |
| 7 | Costs calculated for each system (endoscope, system, maintenance) | Whole colon - high | Costs for each scope calculated as in Appendix 11. |
| 8 | Long-term QALYs derived from SBCS model use alternative utility values | Whole colon - high | Utility values for colorectal cancer derived from Farkkila and colleagues and simulated using SBCS for long-term QALYs (Table 49). |
| 9 | Pooled VCE base case | Whole colon - high |  |
| 10 | NBI, experienced endoscopists | Whole colon - high |  |
| 11 | NBI, experienced endoscopists | Rectosigmoid – high | Only polyps in rectosigmoid colon may be left in situ |
| 12 | Follow-up surveillance | Whole colon - high | Long-term costs and QALYs |
| 1FICE diagnostic accuracy is based only on characterisations in the whole colon made at any level of confidence | | | |

The population for the base case analysis is for patients referred for colonoscopy following bowel cancer screening. Scenario analyses were used to explore two further populations: patients receiving surveillance colonoscopy following previous adenoma removal (referred to as surveillance patients) (scenario 1), and patients referred for colonoscopy for symptoms suggestive of colorectal cancer (symptomatic patients) (scenario 2). We conduct scenario analyses using alternative starting distributions of patients between risk categories to conduct both of these analyses, the alternative values used in these analyses are reported in Section ‎5.4.1.1.

For our base case analysis we used the VC strategy. Three scenario analyses using the DISCARD strategy were conducted with different diagnostic accuracy data used for each. The differences between the VC strategy and the DISCARD strategy are described in Section ‎5.3. Scenario 3 uses diagnostic accuracy data derived from high confidence characterisations in the rectosigmoid colon. Scenario 4 uses diagnostic accuracy data derived from high confidence decisions in the whole colon. Scenario 5 uses diagnostic accuracy data from polyp characterisations made in the whole colon with any level of confidence.

We also conducted a scenario analysis where the VC strategy was applied to the whole colon (Scenario 6), but with diagnostic accuracy data for any level of confidence characterisation instead of diagnostic accuracy from high confidence characterisations in the whole colon (as in the base case); this analysis would represent a worst case scenario on diagnostic accuracy. The diagnostic accuracy data used for Scenarios 3 to 6 are reported in Table 53. All diagnostic accuracy data for NBI and FICE were derived from meta-analyses in Section ‎4.1.2. For i-scan, diagnostic accuracy for the base case and Scenario 4 was derived from our meta-analysis as reported in Section ‎4.1.2, whilst diagnostic accuracy for Scenario 3 was derived from Rath and colleagues,82 and Scenario 5 and 6 were derived from Lee and colleagues.7

Table Diagnostic accuracy data used in scenario analyses

|  | **NBI** | | **FICE** | | **i-scan** | |
| --- | --- | --- | --- | --- | --- | --- |
| **Diagnostic accuracy (colon location – confidence in characterisation)** | **Sensitivity** | **Specificity** | **Sensitivity** | **Specificity** | **Sensitivity** | **Specificity** |
| Rectosigmoid – high confidence1 | 87.41% | 95.26% | 81.39% | 85.02% | 98.10% | 94.40% |
| Whole colon – high confidence2 | 90.97% | 81.88% | 81.39% | 85.02% | 94.34% | 91.53% |
| Whole colon – any confidence level3 | 88.17% | 80.74% | 81.39% | 85.02% | 96.05% | 88.15% |
| 1 Scenario 3 (except FICE); 2 Base case and Scenario 4; 3 Scenario 5 and 6 (and all FICE analyses) | | | | | | |

In the base case analysis, all virtual chromoendoscopy systems have the same cost, as the equipment and maintenance cost for the colonoscopy systems are included in the reference cost of colonoscopy. In this analysis, we investigated the effect on the model results of including the difference in the systems costs compared with the average costs of NBI, FICE and i-scan, using market share data. The net cost differences related to system costs (scope, system and maintenance) from average costs for colonoscopy techniques are reported in Table 54. The calculation of these parameter values is shown in Appendix 11.

Table Net cost difference from the average cost for virtual chromoendoscopy techniques

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Intervention** | **Cost difference** | **95% CI (Lower)** | **95% CI (Upper)** | **Standard Error** |
| NBI | £19.36 | £5.08 | £33.64 | £7.29 |
| FICE | -£61.93 | -£81.22 | -£42.63 | £9.84 |
| i-scan | -£48.27 | -£53.22 | -£43.32 | £2.53 |

Scenario 8 investigates the effect of alternative utility values, derived through our literature review of quality of life studies, have on the model results. The utility values used to generate these long-term outcomes are reported in Table 55, whilst the long-term QALYs produced through by SBCS model for the alternative utility values are reported in Section ‎5.4.1.6.

Table Utility values used in the base case analysis and the scenario analysis

|  |  |  |
| --- | --- | --- |
| **Health state** | **Base Case140** | **Scenario 8140,142** |
| No cancer | 0.798 | 0.798 |
| Colorectal cancer | 0.697 | 0.761 |

Scenario 9 investigates the combined effect ofvirtual chromoendoscopy technologies compared to histopathology. The diagnostic accuracy data for this scenario were taken from our meta-analysis pooling all available studies from high confidence characterisations in the whole colon (described in section ‎4.1.5) and are shown in Table 58. This scenario is based on a post-hoc meta-analysis used to illustrate a possible class effect of the VCE technologies (NB. It features NBI and i-scan studies, but there was insufficient evidence to include FICE).

Scenarios 10 and 11 use diagnostic accuracy data from studies that reported data for endoscopists experienced in the use of NBI. This scenario is informed by a post-hoc meta-analysis of the sub-set of NBI studies in which endoscopists were experienced in the use of NBI for optical characterisation of polyps. This is in contrast to the base case meta-analysis of NBI studies which included studies of experienced and non-experienced endoscopists. Given the observation of higher diagnostic accuracy according to prior experience of the endoscopist this scenario was conducted to provide a more equal comparison with the meta-analysis of i-scan, given that the majority of studies featured experienced endoscopists. These data are shown in Table 56 and the meta-analysis to derive them is described in section ‎4.1.2.

Table Diagnostic accuracy data used in scenario analyses for pooled VCE and experienced endoscopists

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Scenario** | **Sensitivity** | **Specificity** |
| 9 | Pooled VCE base case | 91.82% | 83.20% |
| 10 | NBI, experienced endoscopists (whole colon) | 91.83% | 82.16% |
| 11 | NBI, experienced endoscopists (rectosigmoid) | 90.37% | 98.14% |

In the base case the long-term cost and QALY outcomes, derived from the SBCS model, were estimated assuming the use of standard colonoscopy for any patients requiring follow-up surveillance (i.e. VCE was not used during follow-up colonoscopy). These long-term costs and QALY outcomes do not therefore show the true extent of the future colonoscopies. For example, we would expect there to be future cost savings for virtual chromoendoscopy in any future colonoscopies. We investigated the likely impact on the model results if all patients assigned to the virtual chromoendoscopy group would receive virtual chromoendoscopy technologies for follow-up surveillance (Scenario 12).

The long-term costs and QALYs for the histopathology group were adjusted by an estimate of the differences in costs and QALYs for a follow-up colonoscopy. These were calculated according to the numbers of patients receiving follow-up colonoscopy in each risk group and the additional costs and loss in QALYs at follow-up surveillance, taken from our analysis for the surveillance population (scenario 2, Table 56). From this analysis, the additional cost for each patient receiving histopathology compared to NBI is £84.69 and the loss in QALYs is -0.0007.

We assumed that 20% patients in the low risk group would have a follow-up colonoscopy after 10 years, all intermediate risk patients would have a follow-up colonoscopy after three years and all high risk patients would have a follow-up colonoscopy after one year. Additional costs at colonoscopy were discounted according to how many years until the surveillance colonoscopy. The long-term costs and QALYs for histopathology for the low risk, intermediate risk and high risk groups were then adjusted by the estimates shown in Table 57.

Table Parameters used in follow-up surveillance scenario

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Risk group** | **Proportion receiving follow-up colonoscopy** | **Time until surveillance colonoscopy** | **Additional cost, discounted @ 3.5% pa** | **Additional discounted QALYs** |
| Low risk | 20% | 10 years | £12.01 | -0.00015 |
| Intermediate risk | 100% | 3 years | £76.38 | -0.0007 |
| High risk | 100% | 1 year | £81.82 | -0.0007 |

**Results of scenario analyses**

Pairwise results of the scenario analyses one to eight are reported for histopathology compared to NBI (Table 58), FICE (Table 59) and i-scan (Table 60).

Table Pairwise results for NBI compared to histopathology

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **NBI vs. histopathology** | |  |  |  |  |  |
|  |  | **Histopathology** |  | **NBI** |  |  |
| **#** | **Scenario** | **Costs** | **QALY** | **Costs** | **QALY** | **ICER** |
| *0* | *Base case* | *£988.95* | *11.2703* | *£915.85* | *11.2708* | *Dominated* |
| 1 | Surveillance patients | £925.66 | 11.2684 | £840.97 | 11.2692 | Dominated |
| 2 | Symptomatic patients | £910.75 | 11.2679 | £804.35 | 11.2687 | Dominated |
| 3 | DISCARD, rectosigmoid – high confidence (diagnostic accuracy) | £988.95 | 11.2703 | £946.84 | 11.2703 | Dominated |
| 4 | DISCARD, whole colon – high confidence (diagnostic accuracy) | £988.95 | 11.2703 | £962.08 | 11.2708 | Dominated |
| 5 | DISCARD, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £962.38 | 11.2708 | Dominated |
| 6 | VC strategy, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £914.29 | 11.2706 | Dominated |
| 7 | Costs calculated for each system | £988.95 | 11.2703 | £931.14 | 11.2708 | Dominated |
| 8 | Alternate utility values | £988.95 | 11.2759 | £915.85 | 11.2765 | Dominated |

The scenarios show that NBI dominates histopathology for all scenarios, i.e. NBI is less expensive and more effective.

Table Pairwise results for FICE compared to histopathology

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **FICE vs. histopathology** | |  |  |  |  |  |
|  |  | **Histopathology** |  | **FICE** |  |  |
| **#** | **Scenario** | **Costs** | **QALY** | **Costs** | **QALY** | **ICER** |
| *0* | *Base case* | *£988.95* | *11.2703* | *£901.25* | *11.2701* | *£671,383* |
| 1 | Surveillance patients | £925.66 | 11.2684 | £830.53 | 11.2687 | Dominated |
| 2 | Symptomatic patients | £910.75 | 11.2679 | £794.23 | 11.2684 | Dominated |
| 5 | DISCARD, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £955.93 | 11.2705 | Dominated |
| 7 | VC strategy, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £863.12 | 11.2701 | £963,335 |
| 8 | Alternate utility values | £988.95 | 11.2759 | £901.25 | 11.2759 | £1,273,941 |

FICE has fewer scenario analyses because there is only one source of diagnostic accuracy, a meta-analysis of all FICE characterisations in the whole colon at any level of confidence, which eliminates the possibility of conducting Scenarios 3, 4, or 6. For subgroup analysis for surveillance and symptomatic patients and the DISCARD strategy (scenario 5), FICE dominates histopathology. For scenarios 7 and 8 FICE remains cost effective compared to histopathology.

Table Pairwise comparisons of i-scan to histopathology

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **i-scan vs. Histopathology** | |  |  |  |  |  |
|  |  | **Histopathology** |  | **i-scan** |  |  |
| **#** | **Scenario** | **Costs** | **QALY** | **Costs** | **QALY** | **ICER** |
| *0* | *Base case* | *£988.95* | *11.2703* | *£909.74* | *11.2709* | *Dominated* |
| 1 | Surveillance patients | £925.66 | 11.2684 | £834.99 | 11.2693 | Dominated |
| 2 | Symptomatic patients | £910.75 | 11.2679 | £801.43 | 11.2689 | Dominated |
| 3 | DISCARD, rectosigmoid – high confidence (diagnostic accuracy) | £988.95 | 11.2703 | £949.62 | 11.2706 | Dominated |
| 4 | DISCARD, whole colon – high confidence (diagnostic accuracy) | £988.95 | 11.2703 | £954.70 | 11.2707 | Dominated |
| 5 | DISCARD, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £958.58 | 11.2708 | Dominated |
| 6 | VC strategy, whole colon – any confidence level (diagnostic accuracy) | £988.95 | 11.2703 | £913.85 | 11.2709 | Dominated |
| 7 | Costs calculated for each system | £988.95 | 11.2703 | £860.82 | 11.2709 | Dominated |
| 8 | Alternate utility values | £988.95 | 11.2759 | £909.74 | 11.2766 | Dominated |

For all scenario analyses comparing i-scan to hisopatholgy, i-scan was the dominant strategy.

Scenario 9 shows the analysis for pooled VCE compared to histopathology (Table 61). The results for this scenario are similar to the base case analysis for NBI, and VCE dominates histopathology. For the analysis comparing NBI performed by an endoscopist with prior NBI experience to histopathology, the results are also similar to the base case analyses for NBI and VCE.

Table Scenario analyses for all VCE technologies and for endoscopists experienced in NBI

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **#** | **Scenario** |  | **Costs** | **QALYs** | **ICER (£/QALY)** |
| 9 | Pooled VCE, whole colon, high confidence | Histopathology | £988.95 | 11.2703 | - |
| All VCE | £914.96 | 11.2708 | Dominates |
| 10 | Experienced endoscopists for NBI, whole colon | Histopathology | £988.95 | 11.2703 | - |
| NBI | £916.49 | 11.2708 | Dominates |
| 11 | Experienced endoscopists for NBI, rectosigmoid | Histopathology | £988.95 | 11.2703 | - |
| NBI | £944.69 | 11.2703 | Dominates |

The results for the surveillance scenario where the differences in costs and QALYs between NBI and histopathology in a follow-up colonoscopy were included (Scenario 12), are shown in Table 62. These results are not significantly different to the base case analysis. Compared to the base case analysis, there is an increase in cost savings for NBI of £20 and an increase in incremental QALYs of 0.0003.

Table Results of the follow-up surveillance scenario

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Costs** | **Incremental Costs** | **QALYs** | **Incremental QALY** | **ICER (£/QALY)** |
| Histopathology | £1,011.75 |  | 11.2700 |  |  |
| NBI | £915.85 | -£95.91 | 11.2708 | 0.0008 | Dominates |

* + - 1. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was undertaken to provide estimates of cost-effectiveness and the likelihood of cost-effectiveness under joint uncertainty of parameters. In the probabilistic analysis, costs for colonoscopies are assumed to be identical between technologies. The probabilistic sensitivity analysis was undertaken using 5000 simulations. Cost-effectiveness acceptability curves were created using the net-benefit method to represent the probabilities of interventions being the most cost-effective option across a range of cost-effectiveness thresholds. The parameters and the distributions used in the probabilistic sensitivity analysis are shown in Appendix 9. The choice of distributions used in the PSA is based upon common practice.

**Results**

Table 63 and Figure 38 present the result of the base case analysis using the VC strategy (described in Section ‎5.3).

Table Full incremental probabilistic cost-effectiveness results for virtual chromoendoscopy (base case)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Costs** | **Incremental Costs** | **QALYs** | **Incremental QALYs** | **ICER**  **(£/QALY)** |
| Histopathology | £987.07 | -- | 11.2703 | -- | Dominated |
| FICE | £899.74 | -£87.33 | 11.2701 | -0.0001 |  |
| i-scan | £908.07 | £8.34 | 11.2709 | 0.0008 | £10,298.72 |
| NBI | £914.19 | £6.12 | 11.2708 | -0.0001 | Dominated |

In the base case analysis, i-scan was the most cost-effective technology in 85.2% of analyses at a cost-effectiveness threshold of £20,000 per QALY and in 99.5% of simulations at £30,000 per QALY.

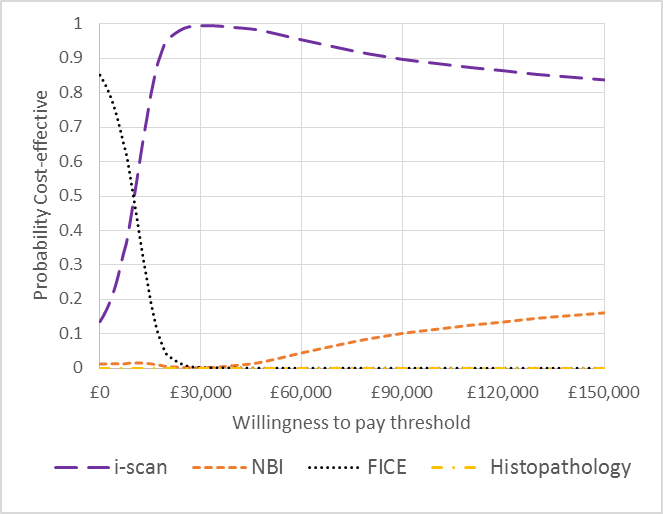


Figure Cost-effectiveness acceptability curves (base case)

* + 1. Comparison of the economic models

Our systematic review of cost-effectiveness identified two previous economic evaluations by Hassan and colleagues111 and Kessler and colleagues.112 Comparing results from these evaluations with our model is difficult, given the differences in design and data used in these studies. Both previous economic evaluations used a similar strategy for virtual chromoendoscopy to that used in our model. They used a resect and discard strategy in the whole colon. Furthermore, Hassan and colleagues included the whole screening population, whereas the population used for Kessler and colleagues and our analysis is for those who had one or more polyps identified. The two previous studies are for a different health care system (USA) and so there are differences in the health state resource costs used between the models. Also the two previous studies have not presented the results in QALYs.

The proportion of low confidence assessments and the diagnostic accuracy data used in the model are shown in Table 64. The sensitivity of NBI used in the model is similar between the studies but we have used a lower specificity than the other models. Kessler and colleagues assumed that all patients would be assessed with high confidence whereas we assume that only 79% of patients are assessed with high confidence.

Table Diagnostic accuracy parameters used in the economic evaluations

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Hassan et al.**111 | **Kessler et al.**112 | **Current assessment** |
| Low confidence assessments | 16% | 0% | 21% |
| Sensitivity NBI | 94% | 90% | 91% |
| Specificity NBI | 89% | 90% | 82% |

All studies concluded that virtual chromoendoscopy would be cost saving compared to histopathology. The cost saved per person was US$174 versus £74 for our model and the model by Kessler and colleagues112 respectively over the patient lifetime.

The expected benefit of resect and discard was 0.0005 years of life in Kessler and colleagues112 compared to 0.0005 QALYs in our model, whilst Hassan and colleagues111 found there was no difference in life expectancy between groups over the patient’s lifetime. The data used for the disease progression to predict life expectancy has not been fully reported in Kessler and colleagues.112 The cost-effectiveness of the submit all strategy compared to resect and discard all polyps varied and was US$377,460 per life year gained for Kessler and colleagues whilst NBI dominated histopathology in our model. Hassan and colleagues were not able to calculate a value as there was no difference in the life expectancy between the submit all and the resect and discard strategy.

1. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

As discussed earlier, it is known that the majority of hospitals that perform endoscopy currently possess endoscopy systems capable of virtual chromoendoscopy. Implementation of the technology will therefore not require large scale replacement of equipment. However, not all systems currently in use comprise fully HD components (i.e. endoscope, light source, video processor, visual display monitor, cabling). Optimum image quality will be attained by fully HD systems, and in some centres this may not be achieved until all equipment is routinely upgraded.

The PIVI statement requires that polyp images taken during virtual chromoendoscopy should be permanently stored and should be of sufficient resolution to support the endoscopists' assessment and clinical decisions.44 Therefore hospitals would need to implement systems to permit adequate electronic storage of HD images linked to patient’s files to allow future re-examination if necessary.

In terms of patient issues and preferences, some patients find colonoscopy to be an uncomfortable experience and therefore may prefer that virtual chromoendoscopy is not used if it may potentially increase the time taken to do the procedure (e.g. the time needed for the endoscopist to inspect the image on the monitor before making a characterisation rather than just resecting it). However, there was very little data from the studies included in our systematic review on differences between procedure times between modes of polyp assessment to provide conclusive evidence.

It is possible that some patients may experience anxiety knowing that a polyp, even one characterised as hyperplastic, has not been resected. Some patients may prefer that all polyps are removed, even when there is negligible risk of them becoming cancerous (notwithstanding the fact that some endoscopists currently leave hyperplastic diminutive polyps in situ, as noted earlier in Section ‎1 of this report). This would not prohibit virtual chromoendoscopy from being used as part of optical assessment, but would mean that a full DISCARD strategy (i.e. leaving in situ hyperplastic polyps in the rectosigmoid) would not be possible for such patients. If a DISCARD strategy is to be implemented there may be a requirement for patient information about the procedure, and the opportunity for discussion between patient and endoscopist before the colonoscopy.

Although virtual chromoendoscopy is currently used in some centres to characterise colorectal polyps its more widespread use would require greater availability of training and auditing to ensure appropriate use. As discussed earlier, current training practices vary in terms of mode and duration, and studies have illustrated the presence of a learning curve to attain acceptable levels of diagnostic accuracy. The manufacturer of NBI suggests that training of up to two days in duration would be sufficient for initial training. However, expert clinical advice suggests that for some endoscopists allocating that amount of time for training might not be realistic due to busy work schedules.

Not all endoscopists may want to assume the responsibility for characterising colorectal polyps and leaving those considered to be hyperplastic in situ. If virtual chromoendoscopy is to be recommended in the NHS there may be a need for awareness raising and incentives to encourage greater acceptance and use of this technology in practice.

1. DISCUSSION
   1. Statement of principal findings
      1. Clinical effectiveness

Thirty studies met the inclusion criteria for the systematic review of test accuracy. These assessed NBI (24 studies), i-scan (5 studies) and FICE (3 studies). Two of these studies assessed two of the technologies of interest in this diagnostic assessment (NBI and i-scan; NBI and FICE). Using the QUADAS criteria, we assessed that the results of the studies are likely to be at a low risk of bias. The evidence we identified meets the decision problem for this diagnostic assessment but there is comparatively little evidence for two of the three technologies being considered (i-scan and FICE). Most of the available evidence evaluated the diagnostic accuracy of NBI for assessing diminutive colorectal polyps. The FICE evidence base was particularly limited. We did not identify any FICE studies that assessed the diagnostic accuracy of endoscopists’ real-time high confidence evaluations of diminutive polyps, whereas we found evidence in relation to high confidence assessments made with NBI and i-scan. Some of the included studies explicitly referred to a DISCARD strategy, while others did not.

Most of the included studies reported high sensitivity and specificity (with some exceptions), showing that endoscopists had a high probability of correctly identifying adenomas and hyperplastic polyps when using NBI, i-scan or FICE (sensitivity and specificity results are discussed in more detail below). NPV (that is, the probability that patients who are diagnosed by virtual chromoendoscopy as having a hyperplastic polyp truly do not have an adenoma) was more variable across the NBI studies than the FICE or i-scan studies. There was especially little variation in this outcome across the i-scan studies, where NPV ranged from 93% to 96.30% for all characterisations and 94.74% to 100% for high confidence characterisations. Of the three technologies, i-scan had the most consistently favourable results on this outcome. The greater heterogeneity found among the NBI studies may in part be explained by the larger pool of evidence available for NBI than i-scan and FICE. Additionally, two of the FICE studies were conducted by the same research group, which may have reduced heterogeneity. The heterogeneity in the NBI results may have also been due to variability in the prevalence of adenomas in the populations included in the studies. When prevalence is increased the result is a decrease in the NPV. The more favourable NPV results found for i-scan and variability among the NBI studies may also be explained by the endoscopists’ experience in these studies. We note that a range of endoscopists was involved in the NBI studies; some were less experienced in conducting colonoscopy generally and had little or no experience using NBI, ranging to others who were very experienced endoscopists who also had extensive experience of using NBI. By contrast, three of the five i-scan studies included endoscopists with prior experience of i-scan and all the studies were conducted in single centres often described as academic or specialist centres. The NPV results found in the i-scan studies may therefore not reflect the accuracy that might be achieved by endoscopists working in more generalist or community settings. On the other hand, the large evidence base for NBI may have captured the variability in this outcome that may be observed in practice, where it is likely endoscopists with a range of experience will carry out colonoscopy (although we note that the ESGE guidance recommends that only experienced and adequately trained endoscopists should undertake virtual chromoendoscopy for the real-time assessment of polyps43).

Table 65 summarises the key sensitivity and specificity results from the review and the meta-analyses, which we now discuss in more detail. Meta-analysis was conducted where possible but the technologies were not assessed head-to-head in the meta-analyses (as this was not within the decision problem for the assessment, derived from the National Institute for Health and Care Excellence scope), so we cannot comment on how the technologies directly compare to each other statistically.

For all characterisations of polyps (regardless of confidence level) in the whole colon the i-scan (1 study) and FICE (3 studies) results were in the same range of values obtained from the NBI studies (17 and 16 studies for sensitivity and specificity respectively). The summary values from bivariate meta-analysis for sensitivity and specificity of NBI and FICE for all characterisations in the whole colon did not reach 0.90 (i.e. 90%) in either case. Limiting the analysis to high confidence characterisations of polyps in the whole colon, increased the summary sensitivity and specificity values from bivariate meta-analysis which were both over 0.90 for i-scan (2 studies) whereas only the summary value for sensitivity was over 0.90 for NBI (11 studies). As mentioned above, none of the FICE studies analysed outcomes for high confidence assessments of diminutive polyps. As with the NPV results, the higher sensitivity and specificity values seen for i-scan might be explained by the endoscopists in the two i-scan studies being experienced endoscopists working in specialist and academic centres. Therefore, a post-hoc analysis restricting the meta-analysis of high confidence characterisations in the whole colon obtained from studies that reported the endoscopists had prior experience with NBI (4 studies) was conducted. The summary sensitivity and specificity results from this post-hoc analysis of NBI were almost identical to those obtained from all the NBI studies.

Some NBI and i-scan studies provided data on characterisations of polyps in the rectosigmoid colon but no evidence was available for FICE. For all characterisations of polyps (regardless of confidence level) in the rectosigmoid colon the NBI (4 studies) and i-scan (2 studies) results were similar to those obtained from the whole colon. Limiting the analysis to high confidence characterisations of polyps in the rectosigmoid colon increased the summary sensitivity and specificity values from bivariate meta-analysis of NBI and the study estimates from i-scan were also higher (meta-analysis was not possible for i-scan). A post-hoc analysis restricting the NBI meta-analysis to high confidence characterisations in the rectosigmoid colon obtained from studies that reported the endoscopists had prior experience with NBI (2 studies) increased the summary sensitivity and specificity values further but there was no evidence for i-scan because the single study that reported on high confidence characterisations in the rectosigmoid colon did not report on whether the endoscopist had prior experience using i-scan.

Overall there is evidence showing that, in general, sensitivity and specificity estimates increase when only high confidence characterisations of polyps are considered compared to when all characterisations are considered (i.e. not on the basis of high confidence). It is worth reiterating that the level of confidence with which polyp classifications are made is subjective and is likely to vary between endoscopists. Some endoscopists may refer to the relevant classification system to make a confident polyp characterisation. The studies included in our systematic review did not explicitly state how confidence was achieved. This creates possible uncertainty in the interpretation of diagnostic accuracy based on high confidence characterisations.

We also generated SROC curves to explore the effect of endoscopist experience with NBI on sensitivity and specificity when characterising polyps in the whole colon. This confirmed that endoscopists with prior experience of using NBI to characterise diminutive colorectal polyps achieve higher sensitivity and specificity than endoscopists with no prior experience of using NBI to characterise diminutive colorectal polyps (other than any training that they undertook at the start of the study). It was not possible to discern this effect when comparing the post-hoc meta-analysis of high confidence characterisations in the whole colon made by endoscopists with prior experience of NBI with the meta-analysis of all high confidence characterisations in the whole colon. This maybe because in the pool of 11 NBI studies providing data on high-confidence characterisations in the whole colon three studies included endoscopists with a mix of prior experience and two did not report on prior experience with NBI which would likely have masked any difference between NBI-experienced (4 studies) and NBI-naive endoscopists (2 studies).

Finally, a post-hoc biviariate meta-analysis pooling together all the available evidence for high confidence characterisations of polyps in the whole colon was undertaken which yielded a sensitivity of 0.92 (95% CI 0.87 to 0.95) and a specificity of 0.83 (95% CI 0.78 to 0.87). There were differing opinions among the clinical experts we consulted regarding whether or not it was appropriate to pool evidence from different virtual chromoendoscopy technologies together. The technologies have the same aim (to enhance surface vessel patterns) but achieve this either by filtering the light source (NBI) or by using digital post-processing software to convert white light images such that they appear like narrow band images (i-scan and FICE). This post-hoc analysis should therefore be treated as illustrative because of the uncertainty regarding whether a class-effect can be assumed and also because the available evidence is predominantly from NBI (11 studies) with only two i-scan studies and none for FICE.

Table Summary of key results

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcome** | **Virtual chromoendoscopy technology** | | |
| **NBI** | **i-scan** | **FICE** |
| All characterisations in the whole colon | | | |
| Sensitivity, range across all studies reporting outcome | 0.55 to 0.97  (17 studies) | 0.95b  (1 study) | 0.74 to 0.88  (3 studies) |
| Sensitivity, bivariate meta-analysis summary value | 0.88 (95% CI 0.83 to 0.92)  (16 studies) | Meta-analysis not possible | 0.81 (95% CI 0.73 to 0.88)  (3 studies) |
| Specificity, range across all studies reporting outcome | 0.62 to 0.95  (16 studies) | 0.86b  (1 study) | 0.82 to 0.88  (3 studies) |
| Specificity, bivariate meta-analysis summary value | 0.81 (95% CI 0.75 to 0.85)  (16 studies) | Meta-analysis not possible | 0.85 (95% CI 0.79 to 0.90)  (3 studies) |
| High confidence characterisations in the whole colon | | | |
| Sensitivity, range across all studies reporting outcome | 0.59 to 0.98  (13 studies) | 0.94 to 0.97c  (2 studies) | No evidence |
| Sensitivity, bivariate meta-analysis summary value | 0.91 (95% CI 0.85 to 0.95)  (11 studies) | 0.96 (95% CI 0.92 to 0.98)d  (2 studies) | No evidence |
| Specificity, range across all studies reporting outcome | 0.44 to 0.92  (12 studies) | 0.90 to 0.92c  (2 studies) | No evidence |
| Specificity, bivariate meta-analysis summary value | 0.82 (95% CI 0.76 to 0.87)  (11 studies) | 0.91 (95% CI 0.84 to 0.95)  (2 studies) | No evidence |
| High confidence characterisations whole colon by endoscopists with prior experience of the technology (post-hoc analysis) | | | |
| Sensitivity, bivariate meta-analysis summary value | 0.92 (95% CI 0.89 to 0.94)  (4 studies) | 0.96 (95% CI 0.92 to 0.98)d  (2 studies) | No evidence |
| Specificity, bivariate meta-analysis summary value | 0.82 (95% CI 0.72 to 0.89)  (4 studies) | 0.91 (95% CI 0.84 to 0.95)d  (2 studies) | No evidence |
| All characterisations in the rectosigmoid colon | | | |
| Sensitivity, range across all studies reporting outcome | 0.84 to 0.90  (4 studies) | 0.90 to 0.94  (2 studies) | No evidence |
| Sensitivity, bivariate meta-analysis summary value | 0.85 (95% CI 0.75 to 0.91)  (3 studies) | Meta-analysis not possible | No evidence |
| Specificity, range across all studies reporting outcome | 0.76 to 0.95  (4 studies) | 0.87 to 0.88  (2 studies) | No evidence |
| Specificity, bivariate meta-analysis summary value | 0.87 (95% CI 0.74 to 0.94)  (3 studies) | Meta-analysis not possible | No evidence |
| High confidence characterisations in the rectosigmoid colon | | | |
| Sensitivity, range across all studies reporting outcome | 0.83 to 0.96  (5 studies) | 0.96  (1 study) | No evidence |
| Sensitivity, bivariate meta-analysis summary value | 0.87 (95% CI 0.80, 0.92)  (4 studies) | Meta-analysis not possible | No evidence |
| Specificity, range across all studies reporting outcome | 0.88 to 0.99  (5 studies) | 0.96  (1 study) | No evidence |
| Specificity, bivariate meta-analysis summary value | 0.95 (95% CI 0.87, 0.98)  (4 studies) | Meta-analysis not possible | No evidence |
| High confidence characterisations in the rectosigmoid colon by endoscopists with prior experience of the technology (Post-hoc analysis) | | | |
| Sensitivity, bivariate meta-analysis summary value | 0.90 (95% CI 0.71 to 0.97)  (2 studies) | No evidence | No evidence |
| Specificity, bivariate meta-analysis summary value | 0.98 (95% CI 0.91 to 1.00)  (2 studies) | No evidence | No evidence |
| **Post-hoc pooled analysis of virtual chromoendoscopy technologies:**  High confidence characterisations in the whole colon | | | |
| Sensitivity, bivariate meta-analysis summary value | 0.92 (95% CI 0.87 to 0.95)  11 NBI studies, 2 i-scan studies | | |
| Specificity, bivariate meta-analysis summary value | 0.83 (95% CI 0.78 to 0.87)  11 NBI studies, 2 i-scan studies | | |

a All characterisations means not separated by endoscopist confidence level.

b One study reported on characterisation of polyps in the distal colon (sensitivity 0.93, specificity 0.83) and one other study reported a per patient analysis of polyps in the last 30 com of colon (sensitivity 0.82, specificity 0.96) but as these outcomes were not for the whole colon they are not directly comparable with the other data in this table row.

c One study reported on high confidence characterisations of distal polyps (sensitivity 0.98 and specificity 0.95) but as these data were not for the whole colon they are not directly comparable with the other data in this table row.

d The ‘High confidence characterisations’ result and the ‘High confidence characterisations by endoscopists with prior experience of the technology’ result are identical because the two studies contributing data to the high confidence meta-analysis were both undertaken by endoscopists with prior experience in using i-scan.

In terms of the other outcomes of interest in this review, none of the studies measured HRQoL, anxiety, number of outpatient appointments or telephone consultations, incidence of colorectal cancer or mortality. Only three of the NBI studies and one of the FICE studies reported AEs (e.g. complications of polypectomy such as bleeding). All reported that there were none. Thus, there is only limited data available on AEs in this review. This is an outcome that future studies should consider measuring. A few of the NBI studies reported on the number of polyps that would be resected and discarded if a resect and discard type of management strategy had been in place. Given the limited evidence available it is challenging to determine the number of polyps that would be designated to be left in place, the number of polyps that would be designated to be resected and discarded, and the number of polyps that would be designated for resection and histopathological examination. Likewise, only limited data were available on the length of time to perform the colonoscopy, which means no firm estimates can be made of the additional time it would take during colonoscopy to make real-time assessments of polyp histology.

Table 66 summarises the results of the studies included in this review in relation to the two PIVI requirements that new technologies for the real-time endoscopic assessment of the histology of diminutive colorectal polyps should meet, before a ‘resect and discard’ strategy could be applied in practice. To reiterate, the criteria specify that for colorectal polyps ≤5 mm in size to be resected and discarded without histopathologic assessment, the endoscopic technology (when used with high confidence) should have a ≥90% agreement in assignment of post-polypectomy surveillance intervals when compared to decisions based on histopathology assessment of all identified polyps. The criteria also specify that in order for a technology to be used to guide the decision to leave suspected rectosigmoid hyperplastic polyps ≤5 mm in size in place (without resection), the technology should provide ≥90% NPV (when used with high confidence) for adenomatous histology (see section ‎1.3). Not all the studies that assessed surveillance intervals evaluated these in accordance with the PIVI criteria. We have therefore only included the results here of those studies that clearly calculated concordance of surveillance intervals between virtual chromoendoscopy and histopathology in line with the PIVI requirements. Neither of the two FICE studies that measured surveillance intervals used the PIVI requirements to do this.83,84 None of the FICE studies examined the NPV for high confidence assessments in the rectosigmoid either. This means that this review did not identify any evidence that enables us to assess how FICE meets the PIVI requirements.

As Table 66 shows, all but one77 of the NBI and i-scan studies that measured surveillance interval assignment in line with the PIVI criteria3,5,6,10-13,68,77,79,82 found a concordance of ≥ 90% between NBI or i-scan and histopathology and thus met this criterion of the PIVI statement (in Ladabaum and colleagues6 only achieved this for one of the two guidelines used to determine surveillance interval). Most studies did not provide a confidence interval, but where this was reported the lower limit fell below 90% in two of six cases. All the NBI and i-scan studies that measured the NPV of high confidence assessments of diminutive polyps in the rectosigmoid found a ≥ 90% NPV, and thus met the second criterion of the PIVI statement. However, NPV and surveillance interval results for i-scan were only provided by one or two studies respectively, and so the evidence in relation to how i-scan meets the PIVI requirements is limited. Our findings suggest that, on the whole, NBI appears to meet the PIVI criteria, supporting the use NBI to carry out a resect and discard strategy in practice. We note that, in general, where there were discrepancies between the surveillance intervals set following NBI and histopathology, NBI surveillance intervals tended to be shorter than they would have been with histopathology (i.e. patients are seen again sooner).

Table Summary of the review’s results in relation to the PIVI criteria

|  |  |  |
| --- | --- | --- |
|  | **Assignment of surveillance intervals in accordance with PIVI** | **NPV (%), for high confidence assessments of diminutive polyps in the rectosigmoid** |
| NBI | 8 of the 9 studies reporting on this outcome achieved a level of agreement that was ≥ 90%. | 92% to 99.4%  (Range across 5 studies) |
| i-scan | 2 of the 2 studies reporting this outcome achieved a level of agreement that was ≥ 90%. | 97.7%  (1 study) |
| FICE | No evidence | No evidence |

It should be noted that our assessment here of the findings of the studies included in this review against the PIVI criteria does not take into account the settings of these studies (i.e. whether they were carried out in specialist, academic settings or routine practice). This could impact on whether virtual chromosendoscopy technologies meet the PIVI criteria. The DISCARD 2 study,145which is a large, multicentre prospective UK study, concluded that NBI cannot be recommended for use in routine clinical practice, as when it is used by non-experts in this setting, it did not result in a high enough concordance rate with histopathology for determining surveillance intervals. This study was not included in our systematic review, as it did not meet the inclusion criteria due to only 22% of the colonoscopies being conducted using HD equipment. In this respect it differs from the studies included in this review and the decision problem for this assessment. It is possible that without HD equipment, diagnostic accuracy and appropriate allocation of surveillance intervals may be lower than that achieved when HD equipment is used.

The results of our systematic review have some similarities to those of previous systematic reviews of virtual chromoendoscopy for characterising colorectal polyps, notwithstanding certain differences between reviews in scope and study inclusion criteria.54-56,146

For example, the American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee conducted a systematic review to examine 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.146 Literature searches were done on a number of standard health research databases, up to May 2014 (thus the search is around two years older than our literature search). For NBI the review included 19 studies giving estimates of NPV and 10 studies giving estimates of agreement in post polypectomy surveillance intervals. For i-scan there were eight studies of NPV and one study of agreement in post polypectomy surveillance intervals. For FICE there were eight NPV studies and two studies of agreement in post polypectomy surveillance intervals. The majority of the studies used high definition endoscopy systems, and some allowed use of magnification (in contrast with our systematic review).

In the ASGE systematic review146 the pooled random effects NPV for studies in which an optical characterisation of diminutive polyps with NBI was made with high confidence was 93% (95% CI, 90%-96%). This increased to 95% (95% CI, 92%-98%) when high confidence characterisations were made by endoscopists experienced in optical assessment of colorectal polyps. In our systematic review the majority of NBI studies reported NPV values for high confidence assessments of over 78%, with five studies reporting NPV values of 90% or more.1,3,5,7,13 (though note that the lower limit of the 95% CI fell below 90% in the majority of studies). The agreement in assignment of post polypectomy surveillance intervals based on optical characterisation of diminutive colorectal polyps with high confidence using NBI was 91% (95% CI, 88%-95%). For i-scan there was no pooled NPV estimate given for high confidence predictions. The overall pooled random effects NPV (any level of confidence prediction) was 84% (95% CI, 76%–91%). A sub-group analysis based on endoscopist experience in performing and interpreting optical biopsies of colorectal polyps reported a pooled random effects NPV of 96% (95% CI, 94-98) for experienced endoscopists compared with a pooled random effects NPV of 72% (95% CI, 69%-76%) for novice endoscopists. As discussed earlier, our systematic review also found that diagnostic accuracy (in terms of sensitivity and specificity) increased in studies (of NBI) involving experienced endoscopists compared to those with less experience. The one i-scan study included in the ASGE review146 which compared surveillance intervals based on optical assessment compared to histopathology reported an agreement level of 69.5% (95% CI, 63%-75%), thus not meeting the PIVI threshold. The overall pooled random effects NPV for FICE was 80% (95% CI, 76%–85%). This estimate did not improve when restricted to studies of endoscopists experienced in use of optical assessment of colorectal polyps.

Another systematic review, reported by Wanders and colleagues,54 assessed the diagnostic performance of virtual chromoendoscopy. This review assessed the sensitivity, specificity and NPV of NBI, FICE, and i-scan for optical diagnosis of colonic polyps (in addition to autofluorescence imaging and confocal laser endomicroscopy, which are not within the scope of our systematic review). Key research databases were searched up to January 2013 (thus three years older than our systematic review). The inclusion criteria were broader than our review, permitting studies of diminutive and larger polyps, studies of real time as well as post-procedure image-based virtual chromoendoscopy, studies with or without magnification, and studies with standard or high definition endoscopy systems. However, sub-group analyses were presented based on these criteria, allowing a comparison more aligned to the scope our systematic review to be made. Pooled bivariate meta-analysis sensitivity for the sub-group of five NBI studies with diminutive polyps where the prediction was made with high confidence was 87% (95% CI 78%-93%) and corresponding pooled specificity was 85% (95% CI 74%-92%). These estimates are reported to have been assessed in the context of the PIVI statement, which implies they are based on characterisations of polyps in the rectosigmoid colon. If this is the case then the corresponding NBI pooled sensitivity and specificity estimates for polyps characterised with high confidence in the rectosigmoid in our bivariate meta-analysis are 87% (95% CI 80%-92%) and 95% (95% CI 87%-98%) respectively (n=four studies). Thus, our estimates are similar in terms of sensitivity but not specificity. A pooled NPV of 83% (95% CI 75%–88%) was reported for NBI, restricted to real time studies (n=35), but not further restricted in terms of diminutive polyps in the rectosigmoid based on high confidence decisions (i.e. in accordance with the PIVI statement), or in terms of the definition status of the endoscopy systems used (standard or high), or magnification status (with or without). The authors suggest that studies of only rectosigmoid NPV are likely to show a good diagnostic performance as the prevalence of non-neoplastic polyps is increased in the rectosigmoid. For FICE bivariate sensitivity and specificity are reported for diminutive polyps, though not stated to be for any particular confidence level (n=four studies). The estimates were 84% (73%-94%) and 87% (79%-94%) respectively, similar to our results (see Table 65). Due to lack of suitable studies no diagnostic accuracy estimates were presented for diminutive polyps characterised with i-scan.

Also of note was that, in the review by Wanders and colleagues,54 sensitivity and specificity did not differ (statistically) significantly according to whether the EXERA or LUCERA NBI system was used. Even though only the LUCERA system is available for use in the UK, the inclusion criteria for our systematic review, based on the National Institute for Health and Care Excellence Scope, allowed studies of both of these systems to be included. (NB. 16 of the NBI studies used EXERA, 5 five used LUCERA and three did not report which system was used – see Table 5). We did not plan to conduct a formal sub-group analyses based on type of NBI system.

* + 1. Cost-effectiveness

A systematic search of the literature found two economic evaluations of virtual chromoendoscopy compared to histopathology. Both studies compared the resect and discard strategy with current practice of submitting all polyps to histopathology. The evaluations were published in USA. The studies found that there were cost savings for the resect and discard group between US$25 and US$174 per person.

A study by Olympus, the manufacturer of NBI, described a budget impact analysis of NBI in NHS England. The decision tree model has a time horizon of seven years and in each year there is a cohort of patients that undergo endoscopy. The study found that NBI offered cost savings of £141 million over seven years.

We developed an independent cost-effectiveness model comparing NBI, FICE and i-scan with histopathology. The base case analysis uses a virtual chromoendoscopy strategy in a bowel screening population where diminutive polyps in the whole colon are optically characterised. The model uses estimates of diagnostic accuracy from our meta-analysis for diminutive polyps characterised with high confidence in the whole colon. The results from our economic model suggest that virtual chromoendoscopy is cost saving compared to histopathology with a mean saving of between £73 and £87 per person over their lifetime. The QALYs are similar between the technologies with a very small increase in QALYs with NBI and i-scan compared to histopathology of between 0.0005 – 0.0007 QALYs per person, while FICE is associated with 0.0001 QALYs fewer per person than histopathology. Virtual chromoendoscopy technologies have a cost saving of about £50 per polyp resection avoided compared to histopathology.The model estimates that the correct surveillance interval would be given to 95% of patients with NBI, 94% of patients with FICE and 97% of patients with i-scan. Results are most sensitive to the pathology cost, the probability of perforation with polypectomy and the proportion of patients who die from perforation. Probabilistic sensitivity analyses were conducted for pairwise and incremental comparisons for histopathology with virtual chromoendoscopy technologies. The probabilistic ICERs were similar to the base case deterministic ICERs. At a willingness-to-pay threshold of £20,000 and £30,000, i-scan was most cost effective in 95% and 33% of simulations respectively.

Analyses were also conducted for a surveillance population, who had previously had one or more adenomas detected at an earlier colonoscopy, and a symptomatic patient population which had been referred for colonoscopy with symptoms suggestive of colorectal cancer. These populations had a lower risk of adenomas than the screening population. All virtual chromoendoscopy technologies were less expensive and more effective than histopathology for the surveillance population and symptomatic population analyses.

Analyses were conducted for a DISCARD strategy where diminutive polyps in the rectosigmoid colon are optically characterised. These analyses used the diagnostic accuracy from our meta-analysis for diminutive polyps characterised with high confidence in the rectosigmoid colon (Figure 16). All virtual chromoendoscopy technologies were less expensive and more effective than histopathology. There were smaller differences in costs and QALYs between virtual chromoendoscopy and histopathology for this analysis than for the base case analysis.

The base case results show that the virtual chromoendoscopy technologies are associated with cost savings compared to histopathology and small gains in QALYs. Given the large number of colonoscopies performed every year, the potential cost savings for the NHS are substantial. The cost savings are due to a reduction in the number of polypectomies performed (with a consequent reduction of adverse events from bleeding and perforation) and polyps sent for histopathological examination. Our base case analysis estimated that there would be around 40% fewer polypectomies performed and this would result in between 3% and 15% of adenomas left in situ with virtual chromoendoscopy and more than 90% fewer hyperplastic polyps resected. The model estimates that virtual chromoendoscopy would lead to incorrect surveillance intervals for between 3% and 6% of patients. The QALY gains are due to the reduction in adverse events, such as perforation, and QALY losses are due to the long-term consequences of not resecting adenomas and patients receiving incorrect surveillance intervals.

The base case analyses indicate that the cost-effectiveness of histopathology compared to virtual chromoendoscopy varies according to the virtual chromoendoscopy technology. The differences in cost-effectiveness between the virtual chromoendoscopy technology are largely attributable to the differences in the diagnostic sensitivity of the technologies, with our meta-analysis calculating sensitivity for i-scan of 0.96 and for FICE of 0.814. We urge caution when comparing between the results of different virtual chromoendoscopy technologies, given the differences in the diagnostic accuracy studies for these technologies in our meta-analyses.

* 1. Strengths and limitations of the assessment
     1. Strengths of the assessment

The strengths of this assessment include that we carried out the systematic review and economic analysis independent of competing interests, and the methods we used were pre-specified in a published protocol. We sought feedback from our expert advisory group on the draft protocol and incorporated their comments into the final version. The protocol was published on the National Institute for Health and Care Excellence website and was discussed by experts in the topic area recruited by National Institute for Health and Care Excellence (specialist members of the appraisal committee). The protocol was also published on the PROSPERO prospective register of systematic reviews website.

We critically appraised all of the diagnostic test accuracy studies included in the review using recognised criteria50,51 to assess potential risks of bias and to assess the generalisability of the results. Our expert advisory group commented on the protocol and a draft of this report, and we also sought specialist methodological input from the NIHR Complex Reviews Support Unit to conduct this assessment.

Our economic model is in line with current BSG108 and ESGE43 guidelines, unlike other models that have examined virtual chromoendoscopy. Hassan and colleagues111 assume that all patients undergoing screening would have a repeat colonoscopy at 10 years, which is not the recommended surveillance interval in BSG or ESGE guidelines. In Kessler and colleagues,112 the polyp groups used are inconsistent with both guidelines. Kessler divides patients into four groups by the types of polyps that patients have, whereas guidelines divide patients into risk groups by the number of adenomas that they have. Solon and colleagues did not examine surveillance intervals, so is not representative of UK practice.116

Our model uses the SBCS model to generate long-term outcomes. The SBCS model was developed for the NHS Bowel Cancer Screening Programme.121 Using long-term outcomes from the SBCS model allows guidance to be consistent across NHS evidence streams.

In line with National Institute for Health and Care Excellence Methodological Guidance,118 we derived as much of our evidence from systematic searches as feasible. The diagnostic accuracy data were obtained from a robust systematic review and meta-analysis using appropriate bivariate meta-analysis techniques, where possible.53 Cost data were derived from appropriate NHS sources, and quality of life data were derived from EQ-5D and expressed in QALYs as the primary measure of benefit. Additionally, we conducted a wide variety of sensitivity analyses to explore uncertainty.

* + 1. Limitations of the assessment

The evidence base for this assessment was particularly limited for FICE and to a lesser extent for i-scan. This limits the conclusions we can draw about the diagnostic accuracy of these technologies for assessing diminutive colorectal polyps in real-time. None of the FICE studies we identified assessed surveillance intervals nor NPV in relation to the PIVI criteria, which meant there was no evidence available to assess how use of FICE meets the PIVI requirements for a resect and discard strategy to be adopted using this technology in practice. Most of the studies included in this review evaluated NBI, but there was heterogeneity in the NBI studies in terms of the original purpose of the studies, country and settings, likely prevalence of adenomas (which can then impact NPV estimates), polyp classification systems used and experience of endoscopists. This makes it difficult to determine the diagnostic accuracy of NBI and to provide clear implications for practice. However, despite this heterogeneity, NBI appears to meet the PIVI requirements (with the caveat that, when reported, the lower limit of 95% confidence intervals was sometimes below the 90% PIVI threshold), supporting its use for a resect and discard strategy in practice.

One limitation of this review is that we did not formally investigate the impact study setting has on diagnostic accuracy estimates. Some research has shown that studies conducted in academic or specialist centres tend find better diagnostic accuracy outcomes than those conducted in generalist settings or community practice.145 It is not possible to determine from this review how accurate NBI is for the real-time diagnosis of diminutive polyps when used in different settings. We also did not formally investigate the impact of the classification system used for characterising polyps in the studies. There was much variation in the reporting of the classification schemes used which would have introduced uncertainty in assembling subgroups. Expert clinical advice suggested that diagnostic performance is unlikely to vary according to different schemes as some of the classification schemes are derived from others (e.g. the NICE) classification1 is based on the Kudo scheme,35 amongst other schemes). Caution is also advised in the interpretation of our subgroup analysis based on endoscopist’s experience with virtual chromoendoscopy, as there was variation between studies in how experience was measured and also there were small numbers of studies in the subgroups.

In order to construct an economic model for histopathology compared to virtual chromoendoscopy, it was necessary to make several assumptions. Firstly, it is not reported in the studies identified how the sensitivity and specificity for individual polyps relates to the surveillance intervals for patients. Whilst some studies in the systematic review of diagnostic accuracy examined correct assignment of surveillance intervals, the data from these studies was insufficient to incorporate in the model. Therefore, we assumed that diagnostic accuracy data for individual polyps was applicable to the entire patient, and assigned patients into risk categories a priori using data from Raju and colleagues.128 When comparing our modelled outcomes to those found in the systematic review of diagnostic accuracy studies, the model’s correct prediction of surveillance intervals was similar to that found in the systematic review (see Section ‎4 for details). Furthermore, we assumed that the prevalence of adenomas was constant across risk groups with adenomas to predict the number of polyps that patients have. It may be that patients in different risk groups have different ratios of adenomas to polyps. If patients with low risk adenomas have a higher number of polyps per adenoma than patients in the higher risk categories, this would adversely affect the cost-effectiveness of histopathology compared to virtual chromoendoscopy, as more hyperplastic polyps would be resected and sent to histopathology.

The long-term cost and QALY outcomes, derived from the SBCS model, were estimated assuming use of standard colonoscopy for any follow-up surveillance. These long-term costs and QALY outcomes do not therefore show the true extent of the future colonoscopies, for example we would expect there to be future cost savings for virtual chromoendoscopy in any future colonoscopies. It was not feasible to include our decision tree within the SBCS model. However, we included a sensitivity analysis to investigate the likely impact of including virtual chromoendoscopy, which had only a small effect on the model results. This was because the majority of patients were low risk, i.e. few of them would have repeat colonoscopy.

The economic analysis includes only diminutive polyps. Although the decision problem focuses on diminutive polyps, some people with diminutive polyps will also have larger sized polyps (falling into the ‘small’ and ‘large’ categories). We attempted to incorporate large and small polyps using data from studies identified in the systematic review and meta-analysis as well as targeted searches, but there was insufficient data to allow coherent analysis of larger polyps. In practice, large polyps would be assessed using only histopathology, and the effect would be an increase the number of patients with intermediate and high risk adenoma (i.e. shorter surveillance intervals), and a decrease in the number of polyps characterised as adenomas in intermediate and high risk patients. It is this last feature of the analysis that made assessing large polyps infeasible as no data were available that indicated the number of polyps found in patients with large polyps at intermediate or high risk. Additionally, no information could be identified on what proportion of patients in the intermediate risk category had two or fewer adenomas with one adenoma being large. Including small polyps would only affect the proportion of patients assessed using only histopathology. Surveillance intervals for small polyps are identical to diminutive polyps.

Further, the model does not differentiate between the type of polyp such as depressed polyps or sessile serrated polyps. No diagnostic accuracy data were identified specifically for either type of polyp. Additionally, sessile serrated polyps are rare and no diagnostic accuracy data were available for diminutive sessile serrated polyps from our systematic review of diagnostic studies (Section ‎4). These polyps may be more likely to be given a low confidence assessment, in which case they would therefore undergo histopathology.

In the absence of data on adverse events for diminutive polyps we have used adverse event rates observed for all polyps. However, this overestimates the number of adverse events as adverse events for diminutive polyps are rarer than for larger polyps. Indeed, comments from our clinical advisors suggest that diminutive polyps are very unlikely to result in perforation. We have varied the adverse event rate in sensitivity analyses (Table 50) where the lower estimate for adverse events for perforation and bleeding was set to zero. With these changes to the adverse event rates, the results are similar to reported in our base case analyses.

Another uncertainty is the variation in diagnostic accuracy of virtual chromoendoscopy that would occur as a result of polyps that are unable to be successfully retrieved for histopathological analysis (e.g. due to fragmentation). We have noted earlier in this report (Section ‎1.2) that histopathology, despite being the accepted reference standard, is imperfect. Evidence shows that polyp retrieval failure increases significantly with smaller polyps, particularly those which are diminutive, even when resected by experienced colonoscopists. Lost polyps would be classified as adenomas, even though many would be hyperplastic. A retrospective analysis of 4383 polyps resected from 1495 patients undergoing colonoscopy in the BCSP reported a polyp retrieval failure rate of 6.1%. In our systematic review estimates of polyps not successfully resected for histopathological analysis, where reported, ranged from 0.5% (Basford)79 to 13% (DISCARD)17 though in most studies estimates were below 5%. The effect of this is to reduce the diagnostic accuracy of histopathology relative to that of virtual chromoendoscopy.17 We note that some polyps resected using the virtual chromoendoscopy strategy would also be sent to histopathology. We have not been able to incorporate this uncertainty into our economic analysis due to lack of data to inform how this would affect all of the relevant input parameters. It may lead to a small reduction in the cost of histopathological assessment due to fewer polyps being sent to the laboratory.

The data on recurrence rates post-polypectomy in the SBCS model have several limitations. The transition probabilities reported in Table 44 are not age-dependent; however, the transition probabilities used in the model are age-dependent. The study populations do not reflect the English bowel cancer screening population, are quite small in size, do not use the BSG surveillance guidelines to categorise adenomas, and report highly varying recurrence rates. The SBCS data on recurrence rates for people classified as intermediate or high risk and undergoing one or three yearly surveillance have not been updated with more recent data from the NHS cancer screening programme.

The full uncertainty around the model results have not been explored in the PSA as the long-term outcome parameters have not been varied. These data were not available from the SBCS model.

* 1. Uncertainties

We considered that the participants enrolled in the NBI, i-scan and FICE studies included in the systematic review of diagnostic accuracy are generally likely to be representative of the types of participants who would receive colonoscopy in the UK for screening, surveillance or on account of symptoms experienced. The majority of the studies were conducted in a single centre and so the results of these studies may not be transferrable to other centres. The endoscopists who took part in the NBI studies had a range of experience with endoscopy and NBI across the studies, and it is unclear how this reflects the experience of endoscopists currently working in UK practice. Endoscopists underwent training in NBI in the majority of the NBI studies but it is unclear how representative this training may be of any received in current UK practice. Relatedly, three of the five i-scan studies were conducted by endoscopists with prior experience of using i-scan, in single centres often described as academic or specialist centres. The results of these studies may therefore not be applicable to less experienced endoscopists working in more generalist or community settings. As we did not explore the effect of the study setting on the results from the NBI studies, it is unclear how generalisable the NBI findings are to specialist and generalist centres in the UK. The European (ESGE) guidance43 recommends that only experienced and adequately trained endoscopists should undertake virtual chromoendoscopy for the real-time assessment of diminutive colorectal polyps. Our review suggests that better diagnostic accuracy (i.e. sensitivity and specificity) outcomes are obtained by more experienced endoscopists, supporting the need for endoscopists to have adequate experience and training in these technologies to use them for real-time diagnosis.

Most of our studies reported diagnostic accuracy derived from expert endoscopists, so the results may not be generalizable to endoscopists with less experience with virtual chromoendosopy technologies. It may be that the level of expertise in endoscopists is lower than in the studies, which would result in lower diagnostic accuracies seen in clinical practice.

The long-term outcomes from the SBCS model include disease progression for patients with small (6-9mm) and large (>10mm) adenomas. It is likely that this overestimates the cancer rates in patients with diminutive polyps who would receive different management due to the use of virtual chromoendoscopy technology. It may be that cancer rates are lower in these patients than predicted by the SBCS model, which would result in lower QALY losses for people treated with virtual chromoendoscopy and therefore increase the cost-effectiveness of histopathology compared to virtual chromoendoscopy.

The FICE diagnostic accuracy data does not include data on polyp characterisations made with high confidence or polyp characterisations made in the rectosigmoid colon, so these cost-effectiveness results are not directly comparable to those of the other virtual chromoendoscopy technologies. More data on the diagnostic accuracy of FICE is necessary to adequately represent its cost-effectiveness.

We have not included within the analysis any benefits to patients in the case where they are informed of the results more quickly or do not have to attend follow-up consultation. There may also be a reduction in anxiety that some patients may experience whilst waiting for results. There was insufficient evidence on these factors to include within the economic analysis.

1. CONCLUSIONS
   1. Implications for service provision

This assessment found that virtual chromoendoscopy technologies (i.e. NBI, i-scan and FICE), using HD systems without magnification, have potential for use in practice for the real-time assessment of diminutive colorectal polyps. The studies identified in this review suggest that, on the whole, NBI and i-scan (when used with high confidence) meet the PIVI requirements for these technologies to be used in practice to carry out a ‘resect and discard’ strategy. Data for i-scan supporting this, though, were limited, and most data were from studies involving endoscopists with prior i-scan experience working in specialist or academic centres. It was unclear how generalisable the NBI results in relation to the PIVI were to UK routine practice settings, as we did not investigate the impact of study setting. Due to limited evidence, it is unclear which of the three virtual chromoendoscopy technologies perform the best. NBI and i-scan had generally better diagnostic accuracy outcomes than FICE, but, again, a greater proportion of i-scan studies were known to involve endoscopists with prior experience of i-scan. Diagnostic accuracy results for NBI were more heterogeneous, but we found that endoscopists with prior experience of NBI achieved higher diagnostic accuracy results than endoscopists with no prior NBI experience and in general when polyp characterisations were made with high confidence diagnostic accuracy was higher. Our findings suggest, as per the ESGE guidance,43 that virtual chromoendoscopy should be undertaken by experienced and adequately trained endoscopists. This has implications for practice in terms of the need to provide training. Virtual chromoendoscopy technologies were cost saving compared to histopathology. NBI and i-scan were more effective than histopathology. FICE was cost effective compared to histopathology.

Uptake of virtual chromoendoscopy for the assessment of diminutive polyps in practice will likely depend on the willingness of colonoscopists to take on the responsibility for characterising polyps and the provision of equipment for NBI, i-scan and FICE. We understand that most endoscopes used in the UK have this technology available, although not all centres may have HD equipment. We did not find any studies measuring patient HRQoL, anxiety or the acceptability of virtual chromoendoscopy to patients, so it is unclear how comfortable patients would be with virtual chromoendoscopy being used to assess their polyps. Some patients may experience anxiety knowing that a hyperplastic polyp has not been resected. Some patients may prefer that all polyps are removed, even when there is negligible risk of them becoming cancerous.

* 1. Suggested research priorities

More research is needed to assess the diagnostic accuracy performance of i-scan and FICE when used without magnification to assess diminutive colorectal polyps in real-time, as there is currently only limited evidence available regarding these two technologies. Ideally any new evaluations of the performance of NBI, i-scan and FICE should be conducted in generalist, routine practice settings, particularly as the i-scan literature is currently limited, and most studies involved endoscopists with prior experience of i-scan working in specialist or academic centres. Multi-centre studies, across a range of settings, would also be informative.

Further studies evaluating the effect of endoscopist experience and training on diagnostic accuracy outcomes when using these technologies would be useful. Endoscopist experience and training is an important consideration and we found few studies that compared the performance of endoscopists with different levels of training and experience, limiting the extent to which we could investigate the influence of this on outcomes in this review.

Future studies should measure adverse effects of polypectomy to provide clearer information about the potential harms of these technologies when used to carry out a ‘resect and discard’ strategy compared to histopathological assessment of all polyps. We suggest that it would be ideal if future studies also included measures of HRQoL and patient anxiety, as it is currently unclear how patients will respond to the use of these technologies in practice.

Longitudinal data from studies following-up patients over time since their colonoscopy procedure was carried out are needed to quantify the impact of these technologies on colorectal cancer incidence, longer-term HRQoL and mortality.

Randomised head-to-head comparisons of NBI, FICE and i-scan would be useful to directly compare outcomes when these technologies are used without magnification to assess diminutive colorectal polyps in real-time. We only identified two head-to-head studies in this review, and so we could only narratively comment on which technologies may perform better. (NB. head to head comparisons of the technologies were not within the decision problem for this assessment, but they may nonetheless be informative to endoscopists interested in using them).

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**Contribution of authors**

Dr Joanna Picot (Senior Research Fellow, evidence synthesis) project managed the study, developed the research protocol, assisted in the development of the search strategy, assessed test accuracy studies for inclusion, performed data extraction and critical appraisal of included test accuracy studies, synthesised evidence including conducting the meta-analyses, drafted and edited the final report.

Mr Micah Rose (Research Fellow, health economics) developed the research protocol, assessed cost-effectiveness and HRQoL studies for inclusion, synthesised evidence, developed the economic model, drafted and edited the final report.

Dr Keith Cooper (Senior Research Fellow, health economics) developed the research protocol, assessed cost-effectiveness and HRQoL studies for inclusion, synthesised evidence, led the development of the economic evaluation, drafted and edited the final report.

Dr Karen Pickett (Research Fellow, evidence synthesis) developed the research protocol, assessed test accuracy studies for inclusion, performed data extraction and critical appraisal of included test accuracy studies, synthesised evidence, drafted and edited the final report.

Professor Joanne Lord (Professorial Fellow in Health Economics) contributed to discussions on the design of the economic model and drafted and edited the final report.

Ms Petra Harris (Research Fellow, evidence synthesis) performed data extraction and critical appraisal of included test accuracy studies, synthesised evidence, drafted and edited the final report.

Dr Sophie Whyte (Research Fellow, health economics) contributed to the development of the economic evaluation, provided data for the economic model, drafted and edited the final report.

Professor Dankmar Böhning (Professor in Medical Statistics) provided training and guidance in the conduct of meta-analyses of diagnostic studies and edited the final report.

Dr Jonathan Shepherd (Principal Research Fellow, evidence synthesis) developed the research protocol, assisted in the development of the search strategy, assessed test accuracy studies for inclusion, performed data extraction and critical appraisal of included test accuracy studies, synthesised evidence, drafted and edited the final report, and acted as the project guarantor.

**Data sharing statement:** All data relevant to this technology assessment report are provided in the accompanying appendices, or may be obtained upon request from the corresponding author. Note that the current report does not include confidential data which were considered during the NICE diagnostics assessment. Confidential data cannot be shared, but their implications for the conclusions of the diagnostic assessment are clearly stated in the current report.

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1. APPENDICES

Appendix Search strategy

The databases we searched for the clinical effectiveness and cost-effectiveness systematic reviews are listed below, along with the search dates.

|  |  |
| --- | --- |
| **Database searched (host)** | **Clinical effectiveness and cost-effectiveness search dates** |
| Combined search on MEDLINE(R) (Ovid) and MEDLINE(R) In-Process & Other Non-Indexed Citations | MEDLINE(R): 1946 – 29/06/2016  MEDLINE(R) In-Process & Other Non-Indexed Citations: searched to 29/06/2016 |
| EMBASE (Ovid) | 1974 – 29/06/2016 |
| Web of Science (all databases) | Searched to 29/06/2016 |
| Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials(CENTRAL)*,* Database of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment database, and NHS Economic Evaluation Database (EED) | Searched to 29/06/2016 |

|  |
| --- |
| **Searched for ongoing trials (all searched on either 12/03/2016 or 13/03/2016)** |
| UK Clinical Trials Gateway (UKCTG) |
| World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) |
| ISRCTN (controlled and other trials) |
| clinicaltrials.gov |
| PROSPERO |

The Medline search strategy for identifying clinical effectiveness and cost-effectiveness publications is shown here. This strategy was adapted for other databases and the other strategies used are available on request.

**Medline search strategy**

1 (virtual and (chromoendoscop\* or "chromo endoscop\*")).tw.

2 ("real time" and (chromoendoscop\* or "chromo endoscop\*")).tw.

3 (video and (chromoendoscop\* or "chromo endoscop\*")).tw.

4 (optical and (chromoendoscop\* or "chromo endoscop\*")).tw.

5 (digital and (chromoendoscop\* or "chromo endoscop\*")).tw.

6 (magnif\* and (chromoendoscop\* or "chromo endoscop\*")).tw.

7 ("image enhanc\*" and (chromoendoscop\* or "chromo endoscop\*")).tw.

8 ("post processing" and (chromoendoscop\* or "chromo endoscop\*")).tw.

9 ("high contrast" and (chromoendoscop\* or "chromo endoscop\*")).tw.

10 ("high performance" and (chromoendoscop\* or "chromo endoscop\*")).tw.

11 ("high definition" and (chromoendoscop\* or chromo endoscop\*)).tw.

12 ("high resolution" and (chromoendoscop\* or "chromo endoscop\*")).tw.

13 (electronic and (chromoendoscop\* or "chromo endoscop\*")).tw.

14 (magnif\* and zoom and imag\*).tw.

15 "real time imag\*".tw.

16 "real time histology".tw.

17 ("real time" and (chromoendoscop\* or "chromo endoscop\*")).tw.

18 "narrow band".tw.

19 NBI.tw.

20 "narrow\* spectrum endoscop\*".tw.

21 "optical diagnosis".tw.

22 "optical imaging".tw.

23 "image enhancement".tw.

24 "EVIS LUCERA".mp.

25 "CV-290/CLV-290SL".mp.

26 "CV-260SL/CLV-260SL".mp.

27 "EVIS EXERA".mp.

28 "dual focus".tw.

29 ("290HQ/290H" and endoscop\*).mp.

30 ("290HQ/290H" and Olympus).mp.

31 ("260Q/260H" and endoscop\*).mp.

32 ("260Q/260H" and Olympus).mp.

33 FICE.mp.

34 flexible spectral imag\* colo?r enhancement.tw.

35 flexible imag\* colo?r enhancement.tw.

36 "white light".tw.

37 "band limited white".tw.

38 "Fuji\* intelligent colo?r enhancement".mp.

39 (Fuji\* adj5 chromoendoscop\*).mp.

40 (Fuji\* adj5 endoscop\*).mp.

41 "Fujinon/Aquilant Endoscop\*".mp.

42 Fuji\* Aquilant Endoscop\*.mp.

43 ("EPX-4450HD" or "EPX3500HD" or "EPX-4400").tw.

44 ((fuji\* and "500 series") or "600 series" or "600 CMOS").tw.

45 "i-scan".mp.

46 "image enhanced endoscop\*".tw.

47 "image enhanced chromoendoscop\*".tw.

48 "image enhanced chromo endoscop\*".tw.

49 (Pentax and endoscop\*).mp.

50 (Pentax and chromoendoscop\*).mp.

51 "EPK i5000".mp.

52 "EPK i7000".mp.

53 "EPK i7010".tw.

54 (Pentax and ("i10" or "90i" or 90K)).mp.

55 ("high definition" and "video processing").tw.

56 or/1-55

57 Colonoscopy/

58 colonoscop\*.tw.

59 Colonic Polyps/

60 (colon\* adj5 polyp\*).tw.

61 (colorectal adj5 polyp\*).tw.

62 Intestinal Polyps/ or Intestinal Polyposis/ or Adenomatous Polyps/

63 (intestin\* adj5 polyp\*).tw.

64 (adenom\* adj5 polyp\*).tw.

65 (diminutive adj5 polyp\*).tw.

66 (small adj5 polyp\*).tw.

67 (hyperplas\* adj5 polyp\*).tw.

68 colo\* lesion\*.tw.

69 colo\* mucosal lesion\*.tw.

70 non neoplastic polyp\*.tw.

71 Colorectal Neoplasms/

72 "colorectal cancer".tw.

73 (colorectal adj2 neoplas\*).tw.

74 "colon\* cancer".tw.

75 (colon adj5 neoplas\*).tw.

76 or/57-75

77 56 and 76

78 ((chromoendoscop\* or "chromo endoscop\*") and polyp\*).ti.

79 polyp\*.tw.

80 nasal polyp\*.tw.

81 Nasal Polyps/

82 80 or 81

83 79 not 82

84 56 and 83

85 77 or 78 or 84

86 limit 85 to animals

87 85 not 86

88 limit 87 to english language

89 remove duplicates from 88

Appendix Study selection worksheet

Study selection took place in two stages:

1) For Title/Abstract screening the following criteria were used

|  |  |  |
| --- | --- | --- |
| PICO element | INCLUSION CRITERIA | EXCLUDE |
| Population | * People with symptoms suggestive of colorectal cancer who are referred for colonoscopy by a GP * People offered colonoscopic surveillance because they have had adenomas removed * People who have been referred for colonoscopy following bowel cancer screening | * people undergoing monitoring for inflammatory bowel disease * people with polyposis syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer), or familial adenomatous polyposis. |
| NOTES: If a mixed population (ie. including one of the excluded groups) then retrieve because results may be presented separately for group(s) of interest. | | |
| Intervention(s) | Real-time and high definition assessment without magnification with one or more of:   * Narrow Band Imaging - EVIS LUCERA ELITE, EVIS LUCERA SPECTRUM and EVIS EXERA (Olympus Medical Systems) * FICE (Fujinon/Aquilant Endoscopy) * i-Scan (Pentax Medical) | Post-procedure assessment |
| NOTES: It may not be clear from title or abstract whether the assessment has been done in real-time or not, whether a high definition system has been used or not and whether magnification has been used or not. If in doubt retrieve for assessment of the full paper. | | |
| Comparator (reference standard) | Histopathological assessment of resected diminutive (≤5 mm) colorectal polyps. (Retrieve any studies stating that white light endoscopy was used as the comparator as this can mean that histopathology was used for diagnosis). |  |
| NOTES: Abstract might not mention histopathology (e.g. might say biopsies taken but not indicate these were for histopathology). Studies of larger sized polyps will be eligible if outcome data are given for the sub-group of diminutive polyps. If in doubt retrieve for assessment of full text paper. | | |
| Outcomes | Any one of:   * Accuracy of assessment of polyp histology (i.e. adenomas; hyperplastic) * Number of polyps left in place * Number of polyps resected and discarded * Number of polyps resected and sent for histological examination * Recommended surveillance interval * Length of time to perform the colonoscopy * Number of outpatient appointments * Health related quality of life (HRQoL) including anxiety * Adverse effects of polypectomy * Colorectal cancer * Mortality |  |
| Study design | RCTs  Prospective longitudinal cohort studies  Cross-sectional studies | If a systematic review then mark as retrieve because these will be used as a source of references  Abstracts: consider retrieving if 2014/2015 or 2016 |

2) For Full text screening - same criteria as applied to titles and abstracts (**ALSO SEE DECISION RULES BELOW**)

|  |  |  |  |
| --- | --- | --- | --- |
| First author, year  Record number: | Reviewer 1: | Reviewer 2: | |
| **Population** | Yes (tick which one(s))  ↓  next question | Unclear  ↓  next Q | No  →  EXCLUDE |
|
| * symptoms suggestive of colorectal cancer referred for colonoscopy by GP |  |  |  |
| * referred for colonoscopy following bowel cancer screening |  |  |  |
| * colonoscopic surveillance because have had adenomas removed |  |  |  |
| **Intervention**  Real-time assessment without magnification using high definition NBI,FICE or i-scan | Yes (tick which one(s))  ↓  next question | Unclear  ↓  next Q | No  →  EXCLUDE |
| * NBI - EVIS LUCERA ELITE, EVIS LUCERA SPECTRUM or EVIS EXERA |  |  |  |
| * FICE |  |  |  |
| * i-scan |  |  |  |
| **Comparator**  Histopathological assessment of resected diminutive (≤5 mm) colorectal polyps. | Yes (all ≤5 mm polyps or results available separately for subgroup)  ↓  next question | Unclear  ↓  next Q | No  →  EXCLUDE |
| *Note: if it appears that the majority of polyps are diminutive (e.g. mean & SD, range, proportion or numbers of diminutive polyps) but no results are available separately continue screening. If a missing separate analysis is the only obstacle to inclusion set on one side for possible future consideration.* | | | |
| **Outcomes** | Yes (indicate which one(s))  ↓  next question | Unclear  ↓  next Q | No  →  EXCLUDE |
| Accuracy of assessment of polyp histology |  |  |  |
| No. of polyps left in place |  |  |  |
| No. of polyps resected and discarded |  |  |  |
| No. of polyps resected and sent for histological examination |  |  |  |
| Recommended surveillance interval |  |  |  |
| Time taken to perform colonoscopy |  |  |  |
| No. of outpatient appointments |  |  |  |
| HRQoL, including anxiety |  |  |  |
| AEs of polypectomy |  |  |  |
| Colorectal cancer |  |  |  |
| Mortality |  |  |  |
| **Study design**   * RCT * prospective longitudinal cohort study * cross-sectional study | Yes  Note which design:  ↓  Final decision | Unclear  ↓  Final decision | No  →  EXCLUDE |
| **FINAL DECISION** | **INCLUDE** | **UNCLEAR** | **EXCLUDE** |

**Decision rules**

During the course of screening full papers issues arose and decision rules have been to deal with these situations.

Population:

* When the population is unclear (i.e. due to lack of description) err on the side of inclusion unless there is definite evidence that the population is one that we are not interested in (e.g. inflammatory bowel disease, polyposis syndromes) [example papers are Hoffman 2010, Rex 2009]
* When population appears to be one we are interested in but paper does not specifically state that the groups we are excluding were not included err on the side of inclusion [example papers are Bashford 2014 and Rath 2015]

Intervention:

Use of inbuilt (close focus) magnification (which will be low level e.g. x1.5) that does not require a zoom endoscope or any other additional equipment can be included. [example paper is Rex 2009]

When use of magnification is described as ‘optional’ but with no further details (i.e. about the level of magnification or the proportion of cases where it was used) err on the side of inclusion. [example paper is Hoffman 2010]

When magnification is not mentioned and no zoom equipment is described err on the side of inclusion (i.e. presume no magnification) [example papers are Bashford 2014 and Rath 2015]

Appendix Data extraction tables

**Aihara et al.67**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:**  Whether a polyp is neoplastic or non-neoplastic. Aim of study was to develop a scoring system for NBI classification of polyps, based on the NBI international colorectal endoscopic classification (NICE), and to assess its performance.  **First author:**  Aihara et al.  **Publication year:**  2015  **Country:**  USA  **Study design:**  Prospective cohort  **Number of centres:**  Not reported, but all authors were affiliated to the same hospital, so it is likely that this was a single centre study.  **Funding:**  Not reported.  **Competing interests:**  One author (CCT) was a consultant for Olympus. The other authors had no competing interests. | **Index test:**  NBI. High definition colonoscope (CF-H180AL, Olympus America Inc, Center Valley PA).  White light was used to initially diagnose the polyp. Then the endoscopist switched to NBI to score the polyp (scores were compared to histopathological diagnoses to determine the threshold score).  **Reference standard:**  Histopathology | | **Number of participants:**  203, of whom 67 were found to have polyps  **Sample attrition/dropout:**  Not explicitly stated, but assumed to be zero.  **Selection of participants:**  See ‘inclusion criteria for study entry’ below.  **Inclusion criteria for study entry:**  Patients presenting for elective screening or follow-up colonoscopy (reason for follow-up colonoscopy not reported).  **Exclusion criteria for study entry:**  None stated. | **Primary outcome of study:**  The threshold score on the polyp scoring system that provided the highest negative predictive value (NPV).  **Other relevant outcomes:**  Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and NPV.  **Recruitment dates:**  Not reported |
| **Participant characteristics** | | | | |
| **Age, years, mean** | 53.7 | | | |
| **Other key patient characteristics (list)** | Patient characteristics of the 67 patients with detected polyps:  Male/female, n (%\*): 43/24 (64.2/35.8).  Polyp size: 121 of the 156 (77.6%\*) detected polyps were sized <5 (NB this does not include polyps sized =5mm, which were classified in the next bracket up: 5-9mm).  Location of the 156 detected polyps also reported (right- or left-sided), but not data extracted.  \*% calculated by reviewer. | | | |
| **Endoscopist experience and training** | Seven endoscopists, described as “experienced”, carried out the colonoscopies. Before the study started, all the endoscopists took part in a training session on NBI interpretation and the scoring system. No further details of experience or training are reported. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | NBI polyp classification system: The Aihara Score modification of the NICE classification (NICE-AS) system. Polyps were classified according to “lesion colour”, “surface pattern” and “vessel pattern”. Polyps that were “light greenish” or “brownish” coloured, had “invisible” or “small round” surface pattern and “invisible” or “slightly dilated” vessel pattern, were classified as non-neoplastic. Polyps that were “deeper brownish”, had “dilated”, “elongated” or “branched” surface pattern and a “dilated” vessel pattern, were classified as neoplastic. Polyps were scored on these factors and could receive a total score of between 0 and 3 (a score of 1 was assigned to each of “lesion colour”, “surface pattern” and “vessel pattern” if a feature suggestive of neoplasia was present).  Pathological diagnoses of sessile serrated adenoma/polyp (SSA/P): The World Health Organisation (WHO) criteria.147 SSA/Ps were classified as neoplastic in the final analysis. None of the three SSA/Ps were <5mm in size. | | | |
| **Sample size calculation** | It was calculated that 138 polyps were needed to allow a 95% confidence limit extend to 85%. This was based on data from a previous ex vivo study which found a diagnostic accuracy of 89% and an assumption that the true accuracy rate would be 90%. 156 polyps were included in the study. | | | |
| **Results – for polyps sized <5mm (i.e. not including those 5mm in size), when using a threshold score of ≥1 on the NICE-AS (indicating at least one feature of neoplasia was present)** | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | **Total** |
| **Index test positive** | (a) 60\* | | (b) 10\* | 70\* |
| **Index test negative** | (c) 2\* | | (d) 49\* | 51\* |
| **Total** | 62\* | | 59\* | 121 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90.1% (95% CIs 84.8 to 95.4) (109 of the 121 polyps were correctly classified) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 96.8% | | 87.3% to 99.4% |
| **Clinical specificity d / (b + d)** | | 83.1% | | 70.6% to 91.1% |
| **PPV a / (a + b)** | | 85.7% | | 74.8% to 92.6% |
| **NPV d / (c + d)** | | 96.1% | | 85.4% to 99.3% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.71\* | | 3.24 to 10.06\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.04\* | | 0.01 to 0.15\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 147.000\* | | 30.755 to 702.62\* |
| Reviewer calculated the same sensitivity, specificity, PPV and NPV values as reported in the paper, but reviewer calculated CIs differed.  \*Calculated by reviewer. | | | | |
| **Interpretability of test** | | Not reported | | |
| **Inter-observer agreement** | | Not reported | | |
| **Intra-observer agreement** | | Not reported | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | |
| **Adverse events** | | Not reported | | |
| **High confidence optical diagnosis** | | Not reported | | |
| **Low confidence optical diagnosis** | | Not reported | | |
| **Number of polyps designated to be left in place** | | Not reported | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | |
| **Recommended surveillance interval** | | Not reported | | |
| **Length of time to perform the colonoscopy** | | Not reported | | |
| **Number of outpatient appointments** | | Not reported | | |
| **Health related quality of life** | | Not reported | | |
| **Colorectal cancer** | | Not reported | | |
| **Mortality** | | Not reported | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Study included patients presenting for elective screening or follow-up colonoscopy, but no further information about the indications for colonoscopy were provided. | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps appeared to receive verification by histopathology. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Pathologists were blinded to the endoscopic findings. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Uninterpretable index test (NBI) results were not reported. | No |
| 11 | Were withdrawals from the study explained? | There appeared to be no withdrawals in this study. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant studies identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The setting and population for this study were unclear, so it is unclear how generalisable the results are to the population of interest in this appraisal and the NHS setting in the UK. All the study endoscopists received training in NBI prior to the start of the study, so the results are applicable to those with some training in NBI. The authors point out that in this study the endoscopists did not diagnose the polyp as such, but scored it on the NICE-AS and point out that the scoring system requires further clinical validation. Different results may have been obtained if the endoscopists had diagnosed the polyp rather than used the scoring system, so the findings may not generalise to other contexts where diagnoses are made using other information or different classification systems. |

**Basford et al.79**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:** Differentiation of adenomas from non-neoplastic polyps  **First author:** Basford et al. The HiSCOPE study  **Publication year:** 2014  **Country:** UK  **Study design:**  Prospective cohort  **Number of centres:**  Single academic hospital (Portsmouth Queen Alexandra)  **Funding:** local departmental research  budget.  **Competing interests:** Stated none | **Index test:**  Pentax EC-3890Li 1.2 Megapixel HD+ colonoscopes, linked to an EPKi processor (Pentax Medical, UK).  Each polyp assessed sequentially by using high definition white light (HDWL) endoscopy followed by i-Scan surface, contrast, and tone enhancement modes (i-Scan 1 = SE  + 3 CE + 4, i-Scan 2 = SE +1, TE colon, i-Scan 3 = SE + 3, CE + 2, TE colon).  **Reference standard:**  Histopathology | | **Number of participants:**  84  **Sample attrition/dropout:**  Not stated  **Selection of participants:**  Patients  attending for colonoscopy through the UK Bowel  Cancer Screening Programme  were prospectively recruited.  **Inclusion criteria for study entry:** Not explicitly stated but appears to be people with a positive faecal occult blood test (FOBT) attending for colonoscopy as part of the UK Bowel Screening Programme.  **Exclusion criteria for study entry:**  Poor bowel preparation, polyposis syndrome, inflammatory bowel disease. Polyps were not included in the study if they were ≥10mm in diameter or if polyp tissue was not retrieved for histologic analysis. | **Primary outcome of study:** overall diagnostic accuracy of high confidence in vivo assessment of small colon polyps (<10 mm)  **Other relevant outcomes:**  specificity and sensitivity for adenomatous histology and  the negative predictive value for adenomatous histology  of diminutive rectosigmoid polyps; The accuracy of prediction  of polyp surveillance intervals based on high confidence in vivo assessment  of all diminutive (<5 mm) colon polyps  combined with histology of polyps  >5 mm  **Recruitment dates:** May 2011 to May  2012 |
| **Participant characteristics** | | | | |
| **Age, years, mean (SD)** | Not stated, but the age range for the UK Bowel Screening Programme is 60 to 74 years. | | | |
| **Other key patient characteristics** | 55 (65%) male, 29 (35%) female (percentages calculated by reviewer).  A total of 209 polyps (up to 10mm in size) were included in the study. Of these, 172 (82%) were ≤ 5mm in size (percentage calculated by reviewer).  Mean polyp size was 4.3 mm, median 4 mm, and standard deviation 2.2 mm. Only 7 of the 209 polyps were pedunculated (0-Ip), with the remainder being sessile (0-Is, n=90) or flat-raised (0-IIa, n=112) according to the Paris classification. A total of 75 of 209 polyps (35.9%) were nonneoplastic, and 134 of 209 (64.1%) were neoplastic. A total of 43% of polyps included were found in the right side of the colon (transverse, ascending, and cecum). | | | |
| **Endoscopist experience and training** | All procedures were performed by a single endoscopist (one of the authors) with experience in in vivo characterisation of colon polyps. Before commencement of the study, the endoscopist underwent a period of familiarisation with the endoscope and imaging technology, including development of a novel classification system for assessment of colon polyps by using i-Scan. It is also stated that the endoscopist was very familiar with the technology and had risen up any learning curve. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | The study useda novelclassification system for assessment of colon polyps byusing i-Scan. This classification system was adapted froma previously described classification system (N.A.C.) (NB. N.A.C is not defined, but references to supporting publications are provided) that was developed for assessment of all colon mucosal lesions. A total of 100 polyps were assessed by the study endoscopist (senior author) documenting features predictive of neoplastic or nonneoplastic histology (as set out in Table 1 and Figure 5 of the journal article). It was validated on a further 100 polyps by 2 other investigators (co-authors) who recorded vascular and surface patterns, which were compared to the final histopathology.  The Paris classification system was used to assess polyp morphology | | | |
| **Sample size calculation** | Prospective sample size calculations were performed with an expected HDWL accuracy of 75% and i-Scan accuracy of 85%. When a power (1-β) of 80% and a 2-sided significance level (α) of 0.05 were used, a total of 198 polyps were required to demonstrate a significant difference between HDWL and i-Scan. A 5% increase was made to allow for lost or nonretrieved specimens, giving a final target of 208 polyps. (NB. The comparison in accuracy between HDWL and i-Scan is not directly relevant to this systematic review). | | | |
| **Results –** sub-set of 172 polyps≤ 5mm in size all characterised with high confidence | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | **Total** |
| **Index test positive** | (a) 100\* | | (b) 7\* | 107\* |
| **Index test negative** | (c) 3\* | | (d) 62\* | 65\* |
| **Total** | 103\* | | 69\* | 172 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 94.2% (95% CI, 92.8% - 99.2%) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 97.1% | | 92.8% - 99.2% |
| **Clinical specificity d / (b + d)** | | 89.9% | | 83.5% - 93.0% |
| **PPV a / (a + b)** | | 93.5%\* | | 87.0% - 97.3%\* |
| **NPV d / (c + d)\*\*** | | 100% | | 93.4% - 100% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 9.57\* | | 4.74 – 19.33\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.03\* | | 0.01 - 0.10\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 295 | | 73.6 - 1184.3 |
| Comments:  \* calculated by the reviewers as values were not reported in the study publication  \*\* recto-sigmoid polyps only (NB. Number of recto-sigmoid diminutive polyps not stated). The NPV for the 2x2 table of 172 diminutive polyps has been calculated by the reviewer and is 95.4% (87.1% to 99.0%) | | | | |
| **Interpretability of test** | | NR | | |
| **Inter-observer agreement** | | NA | | |
| **Intra-observer agreement** | | NR | | |
| **Test acceptability (patients / clinicians)** | | NR | | |
| **Adverse events** | | NR | | |
| **High confidence optical diagnosis** | | Only polyps characterised with high confidence were included in the analysis (n=209). A total of 29 polyps were excluded from the original sample on the basis of low confidence assessment. | | |
| **Low confidence optical diagnosis** | |
| **Number of polyps designated to be left in place** | | NR (but it is believed that all were left in place as authors state that in vivo assessment  was performed in the time between finding a polyp and preparing for polypectomy, therefore implying that polypectomy was always done) | | |
| **Number of polyps designated to be resected and discarded** | | NR | | |
| **Number of polyps designated for resection and histopathological examination** | | NR | | |
| **Recommended surveillance interval** | | Assessed according to American Society of Gastroenterology (ASGE) and British Society of Gastroenterology (BSG) guidelines for adenoma surveillance after colonoscopy. Predicted intervals were compared with those made with histopathology. The patient sample size was 83, due to one patient being excluded because a single polyp was not retrieved for histological analysis.  Surveillance intervals were in agreement with histopathology in 80 of 83 cases with i-Scan  (97.2%) according to BSG guidelines, with identical results for ASGE guidelines. Under i-Scan 2 patients would return earlier and a single patient would have been brought back at 5 years rather than 3 years. | | |
| **Length of time to perform the colonoscopy** | | Not explicitly assessed as an outcome, but the authors report that in vivo assessment was performed in the time between finding a polyp and preparing for polypectomy and did not cause a significant delay. | | |
| **Number of outpatient appointments** | | NR | | |
| **Health related quality of life** | | NR | | |
| **Colorectal cancer** | | NR | | |
| **Mortality** | | NR | | |

NR= Not reported; NA = Not applicable; HDWL = High definition white light HDWL; FOBT = positive faecal occult blood test

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients from the UK Bowel Cancer Screening Programme | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps received verification by histopathology (with the exception of one polyp which was not retrieved for histology) | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Predicted histology was  subsequently compared with the final histopathologic  diagnosis as reported by a Bowel Cancer Screening  Programme–accredited histopathologist who was not  aware of the results of the in vivo assessment | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Of 107 patients screened for inclusion 23 were excluded (19 had no polyps, 2 had inflammatory bowel disease, 2 had stricturing colorectal cancer). | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant studies cited |

|  |
| --- |
| Summary reviewer’s comments |
| The results are applicable to virtual chromoendoscopy with i-Scan conducted in an academic hospital by a colonosopist with extensive prior experience with in vivo polyp characterisation, who was familiar with the i-Scan technology and based only on high confidence assessments. The patients were sampled from the UK bowel screening programme, with apparent FOBT positive results. The authors acknowledge that the study was performed under optimised conditions for in vivo assessment and the high level of accuracy may not necessarily be found in studies without such conditions. |

**Chandran et al.68**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:** The accuracy of real-time endoscopic assessment of diminutive polyps for predicting surveillance intervals.  **First author:**  Chandran et al.  **Publication year:** 2015  **Country:** Australia  **Study design:** Prospective cohort  **Number of centres:** 2 (a tertiary hospital and a private community hospital).  **Funding:** None received.  **Competing interests:** The authors declared they had no conflicts. | **Index test:**  Polyps were identified using an adult or paediatric high-definition, variable stiffness colonoscopies (CF-H180AL or PCF-H180 AL; Olympus Inc., Tokyo, Japan). The study used the high-definition and NBI-compatible Exera processor (Olympus Inc.). Diminutive polyps were examined with NBI without magnification.  **Reference standard:**  Histopathology | | **Number of participants:** 94  **Sample attrition/dropout:** Not explicitly reported, but assumed none (94 patients recruited and results reported for 159 polyps in 94 patients)  **Selection of participants:**  Consecutive patients presenting to the endoscopists involved in the study, who fulfilled in the inclusion criteria below.  **Inclusion criteria for study entry:**  ≥18 years-old; complete colonoscopy; satisfactory or good bowel preparation; at least one polyps sized ≤5 mm.  **Exclusion criteria for study entry:**  Inflammatory bowel disease; primary sclerosing cholangitis; prior colon cancer; poor bowel preparation; and, incomplete colonoscopy. | **Primary outcome of study:**  Diagnostic accuracy of optical diagnosis of diminutive polyps compared with histopathology.  **Other relevant outcomes:**  Accuracy of surveillance intervals assigned following optical diagnosis compared with those assigned following histological assessment (stated secondary endpoint), as per the Preservation and Incorporation of Valuable endoscopic Innovations (PIVI) initiative. Assignment of surveillance intervals was based on NHMRC guidelines (abbreviation not defined in paper) (references provided in paper).  Adverse events (recorded by study investigators) and costs (not included under outcomes). Costs data not extracted.  **Recruitment dates:**  October 2012 to July 2013. |
| **Participant characteristics** | | | | |
| **Age, years, mean (SD)** | Median 62 years (range 19-84). | | | |
| **Other key patient characteristics (list)** | 159 diminutive (≤5 mm) polyps. Median polyp size (range), mm: 3 (1-5).  Female to male ratio of 1.35 (n and %s of each gender not reported).  Colonoscopy indications: previous polyps 32/94 (34%), colon cancer screening 25/94 (26.6%), altered bowel habit 15/94 (16%), rectal bleeding 11/94 (11.7%) and other 11/94 (11.7%).  Polyp location, n/N (%): caecum, 21/159 (13.2%); ascending colon 27/159 (17%); transverse, 30/159 (18.9%); descending, 16/159 (10%); sigmoid, 40/159 (25.2%); rectum, 25/159 (15.7%). | | | |
| **Endoscopist experience and training** | Three endoscopists performed the colonoscopies and they had varying prior experience. One was an interventional endoscopist (M.E.), one a general community gastroenterologist (S.L.) and one an endoscopy fellow (S.C.). Prior to the study, only M.E. had routinely used NBI to assess polyps. All the endoscopists received training in the NBI/Sano-Emura classification system as part of the study. This was a self-study module created for the study, requiring the endoscopists to study an extensive photo library of polyps, a video on NBI classification of polyps and literature about the classification system prior to the study. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | A simplified version of the Sano-Emura classification system was used to classify diminutive polyps: non-adenomatous (type I, no meshed capillaries) and adenomatous (type II, IIIA and IIIB, with meshed capillaries). | | | |
| **Sample size calculation** | A sample size of 146 polyps was calculated to demonstrate a sensitivity of 95% for adenoma detection with a two-sided 95% confidence interval of ±5%. This was based on an expected prevalence of adenomas of 50%. | | | |
| **Results – NBI assessment of diminutive polyps (all study polyps, n = 159)** | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology\*** | **Total** |
| **Index test positive** | (a) 105 | | (b) 11 | 116 |
| **Index test negative** | (c) 3 | | (d) 40 | 43 |
| **Total** | 108 | | 51 | 159 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 91.2%\*\* (145 of 159 polyps predicted accurately) | | | |
| ***Diagnosis\*\*\**** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 97.2% | | 92.1% to 99.4% |
| **Clinical specificity d / (b + d)** | | 78.4% | | 64.7% to 88.7% |
| **PPV a / (a + b)** | | 90.5% | | 83.7% to 95.2% |
| **NPV d / (c + d)** | | 93% | | 80.9% to 98.5% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.51 | | 2.67 to 7.61 |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.0354 | | 0.0115 to 0.109 |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 127 | | 35.3 to 450 |
| \* 51 non-adenomatous polyps, of which 38 were hyperplastic by histopathology, 8 were prominent mucosal folds, 2 inflammatory, 2 sessile serrated adenomas and 1 a leiomyoma.  \*\* Calculated by reviewer.  \*\*\* The sensitivity/specificity, PPV/NPV, positive/negative likelihood ratio and diagnostic odds ratio here are as reported in the study publication. Values calculated by reviewer agree with all the above values with the exception of those for the diagnostic odds ratio. Reviewer calculated a diagnostic odds ratio of 127.3 (CI 33.7 to 480.0).  Diagnostic accuracy results also reported for each of the three endoscopists, but not data extracted here. | | | | |
| **Interpretability of test** | | Not reported. | | |
| **Inter-observer agreement** | | Not reported. | | |
| **Intra-observer agreement** | | Not reported. | | |
| **Test acceptability (patients / clinicians)** | | Not reported. | | |
| **Adverse events** | | Measured but not reported. | | |
| **High confidence optical diagnosis** | | Not reported. | | |
| **Low confidence optical diagnosis** | | Not reported. | | |
| **Number of polyps designated to be left in place** | | Not reported. | | |
| **Number of polyps designated to be resected and discarded** | | Not reported. | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported. | | |
| **Recommended surveillance interval** | | Using the current NHMRC guidelines, 92/94 (98%) patients were correctly allocated to their repeat colonoscopy. The negative predictive value for agreement in assignment of surveillance intervals was 95.7% (95% CI 78.1% to 99.9%). The results were also stratified by endoscopist, and one had a negative predictive value of 88.2% (95% CI 63.6% to 98.5%), which is below the PIVI guidelines threshold. | | |
| **Length of time to perform the colonoscopy** | | Not reported. | | |
| **Number of outpatient appointments** | | Not reported. | | |
| **Health related quality of life** | | Not reported. | | |
| **Colorectal cancer** | | Not reported. | | |
| **Mortality** | | Not reported. | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Yes, the study included all three population groups relevant to this appraisal and who would receive the test in practice. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real-time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Each polyp was resected for histopathological assessment | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Each polyp was assessed by a pathologist blinded to the real time prediction of polyp histology. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Withdrawals not explicitly reported, but believed to be zero. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional relevant studies identified. |

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| --- |
| Summary reviewer’s comments |
| The results reflect the use of NBI in a public and a private hospital setting in Australia, by three endoscopists with varying experience of colonoscopies and NBI, in patients undergoing screening and surveillance colonoscopies, and colonoscopies for symptoms suggestive of colorectal cancer. The population in this study is relevant to the population of interest in this appraisal, and although the reviewer is not aware of how practice in Australia differs to that in the UK, based on the population, the results are likely to be relevant to the UK context. |

**Gupta et al.69**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | | | **Participants** | | | **Outcome measures** | | |
| **Condition being diagnosed / detected:**  The *in vivo* optical diagnosis of colon polyp histology (impact of novel imaging techniques on polyp detection and/or polyp histology prediction)  **First author:** Gupta  [linked publications:  Rastogi et al. 2009;74 Rastogi et al. 2011;88 Rastogi et al 2012.148 119. The reviewer notes that Rastogi et al 2012.148 119 is not a study of NBI so the cited conference abstract148 (which is linked to a full paper119) may not be the correct reference]  **Publication year:** 2012  **Country:** USA  **Study design:** Retrospective analysis of data from 3 prospective clinical trials.74,88,119  Number of centres: In two studies: One centre (Veterans Affairs Medical Center in Kansas City, Missouri). In one study: two centres (Veterans Affairs Medical Center in Kansas City, Missouri and Washington University, St. Louis, Missouri)  **Funding:** Not stated by Gupta et al.69 but stated for the linked publications:  Rastogi et al. 200974 the 2007 Midwest Biomedical research Foundation/Kansas city VA Medical Centre Research Award.  Rastogi et al. 201188 research grant to the primary author from Olympus America Inc.  Rastogi et al 2012148 119) first author supported by Endoscopic Research Career Development award from the American Society for gastrointestinal Endoscopy  **Competing interests (for Gupta et al69):** Drs. Jonnalagadda and Edmundowicz provided consultant work for Olympus America Inc. Dr. Sharma received previous research grants from Olympus America Inc. Dr. Rastogi has received previous research grants from Olympus America Inc and has been supported by the Michael V. Sivak, Jr., MD, Endoscopic Research Award and Endoscopic Research Career Development Award from the ASGE. The other authors disclosed no financial relationships relevant to this publication. | **Index test:**  Histology predicted in real time using NBI without magnification.  In all three studies guessing or predicting the histology based on features other than surface patterns (as described under ‘Polyp classification system’ below) was not permitted.  Commercially available Olypmpus colonoscopes were used (CF-H180AL and PCF-H180AL) in conjunction with the Evis Exera II CV-180 video processor and a 19-inch HD monitor (OEV 191H, Olympus America Inc.) in all three studies.  **Reference standard:**  Histopathology | | | | | | **Number of participants:**  622 participants within the three original trials (total number of participants 1150) met the criteria for this retrospective analysis. Of these 622, 410 (65.95%) had a least 1 polyp detected and resected.  Total number of polyps n=1254  **Sample attrition/dropout:**  An in vivo optical diagnosis could not be determined for 4 polyps (0.3%) (histology showed three to be adenomatous and the other one hyperplastic).  **Selection of participants:**  To identify data for this study the central database holding the data for all 3 trials was queried to identify all subjects who had colonoscopy with high-definition white light or NBI and who had in vivo prediction of polyp histology for every polyp detected by NBI. Participants with an endoscopically malignant-appearing mass or whose resected polyp could not be retrieved for histopathology were excluded.  Inclusion and exclusion criteria for the trials themselves were the same for all 3 trials:  **Inclusion criteria for study entry:**  Participants were referred and scheduled for screening or surveillance colonoscopy and the ability to provide informed consent.  **Exclusion criteria for study entry:**  previous surgical resection of any part of the colon, history of colon cancer, history of inflammatory bowel disease, use of antiplatelet agents or anticoagulants that would prevent removal of polyps, poor general condition or any other reason to avoid prolonged procedure time, history of polyposis syndrome or hereditary nonpolyposis colon cancer, or the inability to give informed consent.  Potential participants with inadequate bowel preparation or in whom the caecum could not be reached during the procedure were excluded. | | | **Primary outcome of study:**  Accuracy in predicting colonoscopy surveillance intervals, negative predictive value for diagnosing adenomatous histology in the rectosigmoid part of the colon.  **Other relevant outcomes:**  sensitivity, specificity and overall accuracy of in vivo optical diagnosis in differentiating adenomas from non-adenomas, the reduction in the number of polyps sent for histopathology, cost savings.  **Recruitment dates:** November 2007 to October 2010 (recruitment in 1 of 3 clinical trials). | | |
| **Participant characteristics** (for the 410/622 (65.9%) patients who had at least one polyp detected and resected) | | | | | | | | | | | | |
| **Age, years, mean (SD)** | 61.7 (8.1) | | | | | | | | | | | |
| **Other key patient characteristics (list)** | Male n=367 (89.5%)  White n = 314 (76.6%)  History of polyps n=145 (35.4%)  Family history of colon cancer n=23 (5.6%) | | | | | | | | | | | |
| **Endoscopist experience and training** | The colonoscopies in all three of the trials were performed by six experienced endoscopists (3 at each centre). Each endoscopist had performed >3000 colonoscopies and all had experience of high-definition white light endoscopy and NBI.  Rastogi et al. 200974 involved just one endoscopist (the lead author) described as ‘experienced’.  In the Rastogi et al. 201188 study the lead investigator reviewed the surface mucosal and vascular patterns used for polyp prediction with NBI with the five other study endoscopists. Images of 50 polyps viewed with NBI were discussed in detail in a structured teaching session until all investigators were confident in their recognition. | | | | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Location, size and morphology of each polyp detected were documented. Polyp location and size were characterised using the same method in each of the 3 studies. Polyp morphology was classified as follows:  Rastogi et al. 200974 used the Paris Classification  Rastogi et al. 201188 and  Rastogi et al 2012119,148 used a classification described by the Japanese Society for Cancer of the Colon and Rectum149  For histology prediction with NBI each polyp was assessed for surface mucosal and vascular patterns and then classified as type A (consistent with hyperplastic polyp) or type B (consistent with an adenoma):  Type A   * Fine capillary network alone but absent mucosal pattern * Circular pattern with dots - pattern with central dark area surrounded by clear lighter area   Type B   * Round/oval pattern - central light area surrounded by dark outer area * Tubulogyrus pattern - presence of tubules, either linear or convoluted.   Rastogi et al. 200974 indicates that where polyps had both a Type A pattern and a Type B pattern they were classified as Type B. Polyps with surface patterns that were neither Type A nor Type B were classified as miscellaneous and if a clear pattern could not be visualised the category was ‘not identified’. If a surface pattern was ‘not identified’ then the histology could not be predicted.  Rastogi et al. 200974 state that histopathological assessment was performed using the Vienna classification (no further details or reference provided). | | | | | | | | | | | |
| **Sample size calculation** | None provided for this retrospective analysis but provided for the primary outcome of each of the original clinical trials. | | | | | | | | | | | |
| **Results: For subgroup of polyps ≤5mm in size (n=884)** | | | | | | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | | | | **Hyperplastic polyps on histopathology** | | | **Total** | | |
| **Index test positive** | 484 \* (a) | | | | | | 97 \* (b) | | | 581 \* (a+b) | | |
| **Index test negative** | 37 \* (c) | | | | | | 266 \* (d) | | | 303 \* (c+d) | | |
| **Total** | 521 \* (a+c) | | | | | | 363 \* (b+d) | | | 884 (a+b+c+d) | | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 84.8% (95% CI 82.3 to 87.1) | | | | | | | | | | | |
| \* = calculated by reviewer | | | | | | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | 92.9% | | | | | | 90.3 to 94.9 | | |
| **Clinical specificity d / (b + d)** | | | | 73.3% | | | | | | 68.5 to 77.8 | | |
| **PPV a / (a + b)** | | | | 83.3% \* | | | | | | 80.0% to 86.3% \* | | |
| **NPV d / (c + d)** | | | | 87.8% \* | | | | | | 83.6% to 91.3% \* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | 3.48 \* | | | | | | 2.93 to 4.13 \* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | 0.01 \* | | | | | | 0.07 to 0.13 \* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | 35.87\* | | | | | | 23.87 to 53.90 \* | | |
| \* = calculated by reviewer. Using the reviewers’ imputed values for the 2x2 table yields almost identical point estimates and 95% CIs as reported in the paper. | | | | | | | | | | | | |
| **Results: For subgroup of polyps ≤ 5mm and located on the left-side side of the colon** | | | | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | | | | **Hyperplastic polyps on histopathology** | | | | **Total** |
| **Index test positive** | | 191 \*(a) | | | | | | 67 \*(b) | | | | 258 \*(a+b) |
| **Index test negative** | | 18 \*(c) | | | | | | 240 \*(d) | | | | 258 \*(c+d) |
| **Total** | | 209 \*(a+c) | | | | | | 307 \*(b+d) | | | | 516 (a+b+c+d) |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 83.5% (95% CI 80.0 to 86.6) | | | | | | | | | | |
| \* = calculated by reviewer | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | **Value** | | | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | | | | 91.4% | | | | 86.8 to 94.8 | | | |
| **Clinical specificity d / (b + d)** | | | | | 78.1% | | | | 73.0 to 82.6 | | | |
| **PPV a / (a + b)** | | | | | 74.03% \* | | | | 68.23% to 79.27% \* | | | |
| **NPV d / (c + d)** | | | | | 93.02 % \* | | | | 89.20% to 95.81% \* | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | 4.19 \* | | | | 3.37 to 5.20 \* | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | 0.11 \* | | | | 0.07 to 0.17 \* | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | 38.01 \* | | | | 21.84 to 66.14 | | | |
| \* = calculated by reviewer. Using the reviewers’ imputed values for the 2x2 table yields almost identical point estimates and 95% CIs as reported in the paper. | | | | | | | | | | | | |
| **Results: For subgroup of polyps ≤ 5mm and located in the rectosigmoid part of the colon** | | | | | | | | | | | | |
|  | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | | | |
| **Index test positive** | | | not reported (a) | | | not reported (b) | | | not reported (a+b) | | | |
| **Index test negative** | | | 11 \*(c) | | | 226 \*(d) | | | 237 (c+d) | | | |
| **Total** | | | not reported (a+c) | | | not reported (b+d) | | | not reported (a+b+c+d) | | | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | not reported | | | | | | | | | |
| \* = calculated by reviewer. States that of the 237 diminutive polyps in the rectosigmoid that were predicted to be non-adenomatous, 3 (1.3%) were found to be adenomas with advanced histologic features (any villous component or high-grade dysplasia) however, in order to obtain the NPV of 95.4% reported there should have been 11 diminutive polyps in the rectosigmoid which were predicted to be non-adenomatous but found to be adenomas by histology (and it is presumed that it is 3 of these 11 that then had the advanced histologic features). Insufficient data were reported to enable this 2x2 table to be reconstructed. | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | | | | not reported | | | | | not reported | |
| **Clinical specificity d / (b + d)** | | | | | | not reported | | | | | not reported | |
| **PPV a / (a + b)** | | | | | | not reported | | | | | not reported | |
| **NPV d / (c + d)** | | | | | | 95.4% | | | | | 91.8 to 97.7 | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | not reported | | | | | not reported | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | not reported | | | | | not reported | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | not reported | | | | | not reported | |
| **Interpretability of test** | | | | Not reported | | | | | | | | |
| **Inter-observer agreement** | | | | Not applicable | | | | | | | | |
| **Intra-observer agreement** | | | | Not applicable | | | | | | | | |
| **Test acceptability (patients / clinicians)** | | | | Not reported | | | | | | | | |
| **Adverse events** | | | | Not reported | | | | | | | | |
| **High confidence optical diagnosis** | | | | Not reported | | | | | | | | |
| **Low confidence optical diagnosis** | | | | Not reported | | | | | | | | |
| **Number of polyps designated to be left in place** | | | | Not reported | | | | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | Table 4 in the paper provides values for the reduction in polyps requiring histopathology for various hypothetical predict, resect and discard strategies. One of these is for diminutive polyps (n=884/1254 polyps discarded without histopathology, 70.5% reduction) but not limited to the rectosigmoid colon. States “Using this strategy, 13 adenomas (1.5%) with advanced histologic features (any villous component or high-grade dysplasia) would be discarded.” The reviewer assumes the ‘this strategy’ referred to is a ‘predict, resect and discard’ strategy and from the values given this must relate to diminutive polyps only. | | | | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | Not reported | | | | | | | | |
| **Recommended surveillance interval** | | | | The Joint Guidelines developed by the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology were used to calculate surveillance intervals based on in vivo optical diagnosis and histopathology. Two surveillance interval groups (A and B) were calculated:  A] colonoscopy in 3 years for patients with 3 or more adenomas or 1 or more advanced (≥10 mm, villous histology, or high-grade dysplasia) adenomas, 5 years for patients with 1 to 2 small (<10 mm) adenomas without advanced histology, and 10 years for patients with no adenomas  B] colonoscopy in 3 years for patients with 3 or more adenomas or with 1 or more advanced adenomas and 10 years for patients with 1 to 2 small adenomas or no adenomas.  Recommendations for surveillance intervals based on the in vivo optical diagnosis were generated only for the patients with at least one polyp. An analysis was conducted limited to the in vivo diagnosis of all diminutive polyps and surveillance intervals were predicted correctly in 86.1% (95% CI 82.4 to 89.3) for surveillance interval A. For surveillance interval B 94.1% (95% CI 91.4 to 96.2) of surveillance interval predictions were correct.  Three hypothetical strategies led to higher accuracy rates than the predict, resect and discard strategy for diminutive polyps only. These three strategies were:  1) right-sided colon polyps only (93.6% and p≤0.0001 for surveillance interval A; 97.8% and p=0.003 for surveillance interval B)  2) flat lesions only (97.3% and p < 0.0001 for surveillance interval A; 98.8% and p=0.003 for surveillance interval B)  3) diminutive polyps in the left-sided colon only (91.0% and p <0.0001 for surveillance interval A; 95.6% and p =0.03 for surveillance interval B).  Two other hypothetical predict, resect, and discard strategies had higher accuracy rates for surveillance interval A (but not surveillance interval B) compared with the predict, resect, and discard strategy for all diminutive polyps only. These two strategies were:  1) left-sided colon polyps only (89.0% and p=0.03)  2) diminutive and small left-sided colon polyps only (89.3% and p=0.01). | | | | | | | | |
| **Length of time to perform the colonoscopy** | | | | Not reported | | | | | | | | |
| **Number of outpatient appointments** | | | | Not reported | | | | | | | | |
| **Health related quality of life** | | | | Not reported | | | | | | | | |
| **Colorectal cancer** | | | | Not reported | | | | | | | | |
| **Mortality** | | | | Not reported | | | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | The three studies that provided data for this analysis enrolled participants referred and scheduled for screening or surveillance colonosocopy. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Reference standard was histology | Yes |
| 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? | Polyps excised for histology at the time of index test. | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The pathologist was blinded to the optical diagnosis | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histology results not available at time of index test. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | An optical diagnosis could not be determined for 4 polyps (0.3%). | Yes |
| 11 | Were withdrawals from the study explained? | This retrospective analysis included 622 of 1150 patients from 3 trials who met the inclusion criteria for the retrospective analysis therefore no participants were able to withdraw. | n/a |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes (and for the two linked papers on NBI), no additional papers identified. |

|  |
| --- |
| Summary reviewer’s comments |
| Each of the endoscopists involved were experienced although it is not clear how experienced they were in the use of NBI. The participants were eligible for screening or surveillance and the majority were white men. The results may not be applicable to less experienced endoscopists and more diverse samples of participants. |

**Henry et al.70**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:** Efficacy of NBI without optical magnification for differentiating neoplastic from non-neoplastic colorectal polyps, using meshed capillary (MC) pattern.  **First author:** Henry et al.  **Publication year:** 2010  **Country:** USA  **Study design:** Retrospective comparison of prospectively collected data.  **Number of centres:** 1 (academic medical centre)  **Funding:** Not stated.  **Competing interests:** Three authors disclosed consultant relationships with Olympus. One disclosed grant support from Boston Scientific, Alveolus, ConMed, and Cook Medical. The remaining authors disclosed no financial conflicts. | **Index test:**  High definition (HD), adult or pediatric, variable-stiffness colonoscope (CF-H180AL or PCF-H180AL, Olympus America, Center Valley, Penn). Processor capable of NBI and HD imaging (EVIS Exera II CV-180; Olympus America).  Polyps had been previously identified with white light HD colonoscopy and were examined with NBI and up to 1.5X digital zoom (without true optical magnification).  **Reference standard:**  Histopathology | | **Number of participants:**  33 (total sample; number of participants in the diminutive polyp subgroup analysis not reported)  **Sample attrition/dropout:**  Not reported, but likely to be zero as this was a retrospective study of prospectively collected data and all participants that met the inclusion criteria were likely to have been included.  **Selection of participants:**  A retrospective review of endoscopy logs identified consecutive patients who had undergone colonoscopy with NBI and polypectomy at the study centre for potential inclusion in the study.  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  No polyps identified; a polyp diagnosis was made before colonoscopy from a biopsy sample; and, active inflammatory bowel disease. | **Primary outcome of study:**  Not described as primary, but main outcome measurements: Sensitivity, specificity, PPV, NPV, and diagnostic accuracy.  **Other relevant outcomes:**  No others reported.  **Recruitment dates:**  October 2008 to March 2009. |
| **Participant characteristics** | | | | |
| **Age, years, mean (SD)** | Median 59.5 years (range 34-84 years) (total sample). | | | |
| **Other key patient characteristics** | Male, n = 33/52 (63.5%) (total sample).  Colonoscopy indications, n (%\*): screening for colorectal adenoma and cancer, 15 (28.8%); surveillance of patients with prior colorectal adenomas, 22 (42.3%); prior colorectal cancer, 1 (1.9%); symptoms suggestive of colorectal cancer, 14 (26.9%). \*All %s calculated by reviewer. (Total sample.)  A total of 126 polyps were identified (total sample). Median size 3mm (range 2-30mm). Location, n: cecum, 12; ascending colon, 24; hepatic flexure, 5; traverse colon, 17; descending colon, 11; sigmoid colon, 24; rectosigmoid colon, 12; rectum, 21. Morphology (Paris type), n: 0-Is, 30; 0-Ip, 7; 0-IIa, 82; the remaining polps were classified as 0-IIb, 0-IIc, 0-IIa + IIc, 0-IIa + Is, 1 and 3 (n = 7) – the exact number of polyps classified into the categories is provided in the paper but not data extracted here. Histopathology, n (%\*): neoplastic, 67 (53%); non-neoplastic, 59 (47%). The neoplastic classification included the following histopathologies: adenoma (low grade), tubovillous adenoma, adenocarcinoma, and squamous cell carcinoma. The non-neoplastic classification included the following histopathologies: hyperplastic, normal mucosa, and inflammatory. The number of polyps classified into each histopathology subcategory is provided in the paper but not data extracted here.  90 of the 126 polyps (71.4%\*) were sized ≤5mm.  Subgroup analyses by polyp size: ≤5mm, 6 to 9mm, ≥10mm and ≥6mm (which included the previous two size categories). Only ≤5mm data extracted.  \*% calculated by reviewer. | | | |
| **Endoscopist experience and training** | An endoscopist who had received training in NBI and chromoendoscopy either performed or supervised each colonoscopy. The endoscopist’s training consisted of lectures, self-study and a 1-week intensive course that involved performing or participating in over 50 NBI and chromoendoscopy examinations. No information is provided about the endoscopist’s previous experience in carrying out colonoscopies. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | During the colonoscopy and before polypectomy, the Sano-Emura classification (references provided in the paper91,92) was used to classify polyps as having neoplasia or as being non-neoplastic, based on the appearance of the MC vessels. Neoplasia (including Sano-Emura type II, IIIA, and IIIB patterns) was denoted by a polyp being MC positive. Non-neoplastic polyps (including Sano-Emura type I pattern) were denoted by a polyp being MC negative.  After the colonoscopy, the Paris classification was used to classify the number, location and size of polyps found and resected, based on endoscopic photographs. | | | |
| **Sample size calculation** | Not reported. | | | |
| **Results – NBI for polyps sized ≤5mm** | | | | |
|  | **Adenomatous\* polyps on histopathology** | | **Hyperplastic\*\* polyps on histopathology** | **Total** |
| **Index test positive** | (a) 32 | | (b) 4 | 36 |
| **Index test negative** | (c) 5 | | (d) 49 | 54 |
| **Total** | 37 | | 53 | 90 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90.0% (95% CI, 82% to 95%) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 86.5% | | 70% to 95% |
| **Clinical specificity d / (b + d)** | | 92.5% | | 81% to 98% |
| **PPV a / (a + b)** | | 88.9% | | 73% to 96% |
| **NPV d / (c + d)** | | 90.7% | | 79% to 97% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 11.46\*\*\* | | 4.43 to 29.66\*\*\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.15\*\*\* | | 0.06 to 0.33\*\*\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 78.400\*\*\* | | 19.563 to 314.198\*\*\* |
| Reviewer’s calculations of sensitivity, specificity, PPV and NPV generally agree with those reported in the paper, but some values and 95% CIs marginally differ: sensitivity = 86.49% (95% CI, 71.23% to 95.46%), specificity = 92.45% (95% CI, 81.79% to 97.91%), PPV = 88.89% (95% CI, 73.49% to 96.89%), and NPV = 90.74% (95% CI, 79.70% to 96.92%).  \* Neoplastic.  \*\* Non-neoplastic.  \*\*\* Calculated by reviewer. | | | | |
| **Interpretability of test** | | Not reported | | |
| **Inter-observer agreement** | | Not reported | | |
| **Intra-observer agreement** | | Not reported | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | |
| **Adverse events** | | Not reported | | |
| **High confidence optical diagnosis** | | Not reported | | |
| **Low confidence optical diagnosis** | | Not reported | | |
| **Number of polyps designated to be left in place** | | Not reported | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | |
| **Recommended surveillance interval** | | Not reported | | |
| **Length of time to perform the colonoscopy** | | Not reported | | |
| **Number of outpatient appointments** | | Not reported | | |
| **Health related quality of life** | | Not reported | | |
| **Colorectal cancer** | | Not reported | | |
| **Mortality** | | Not reported | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | All but one of the included patients were undergoing colonoscopy for screening for colorectal adenoma and cancer, for surveillance due to prior colorectal adenomas, or to investigate symptoms suggestive of colorectal cancer. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real-time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps received verification by histopathology. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The paper does not provide information about whether the pathologist was blinded to the NBI prediction. | Unclear |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Not stated but believed to be zero. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant studies cited. |

|  |
| --- |
| Summary reviewer’s comments |
| All but one of the included patients were undergoing colonoscopy for screening for colorectal adenoma and cancer, for surveillance due to prior colorectal adenomas, or to investigate symptoms suggestive of colorectal cancer. The findings from this study are therefore very relevant to the patient population of interest in this appraisal. However, patients were from the USA and it is unclear how representative of UK patients they are. Also, the study included a small number of patients (n = 33) in the diminutive polyp subgroup analysis and it is unclear if a larger sample would give the same findings. No sample size calculation was reported, so it is unclear if the analysis was adequately powered. The study was carried out at one centre and one endoscopist was involved in the study colonoscopies. The endoscopist had received training in NBI, but it is unclear how experienced he was in carrying out colonoscopies. The results may not be applicable to a wider range of settings or endoscopists who have not received training in NBI. |

**Hewett et al. 2012a2**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | | **Outcome measures** |
| **Condition being diagnosed / detected:** Differentiation of adenomatous and hyperplastic polyps in the distal colon. Aim of study was to assess feasibility of leaving hyperplastic polyps in the distal colon in place.  **First author:** Hewett et al.  **Publication year:** 2012  **Country:** USA  **Study design:** Prospective cohort (described as a ‘prospective observational study’ by the authors)  **Number of centres:** 1 (a university hospital and its affiliated ambulatory surgery centre, described by authors as a single centre)  **Funding:**  Not stated.  **Competing interests:**  Two of the authors disclosed a consultant relationship with Olympus Medical Systems Corporation, Tokyo, Japan. The other author has received research support from Olympus America, Inc. | **Index test:**  High definition NBI without optical magnification (CF180AL, Evis Exera II; Olympus America).  When a polyp was detected in white light in the sigmoid colon or rectum, NBI was used to examine the surface characteristics. Electronic magnification (X 1.5) was used as needed.  **Reference standard:**  Histopathology | | **Number of participants:**  225 patients underwent colonoscopy; of these 31 had a total of 240 rectosigmoid polyps. A total of 235 polyps were included in the overall analyses; 220 (98%; reviewer calculates 93.6%, so this appears to be an error in the paper) polyps were included in the in the diminutive polyp (≤5mm) subgroup analysis (number of patients not stated).  **Sample attrition/dropout:**  None reported.  **Selection of participants:**  Consecutive adult patients having elective screening or surveillance colonoscopy for “standard indications” (p. 375).  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  History of colectomy, inflammatory bowel disease, or polyposis syndrome. | | | **Primary outcome of study:**  Sensitivity and negative predictive value of high-confidence predictions of histology.  **Other relevant outcomes:**  Diagnostic accuracy, specificity and predictive values.  **Recruitment dates:** Not stated. |
| **Participant characteristics – total sample (n = 31, 235 distal colorectal polyps).** | | | | | | |
| **Age, years, mean (SD), median** | 59.6 (9.8), 59. | | | | | |
| **Other key patient characteristics (list)** | Gender, n/N (%): male 16/31 (52); female 15/31 (48).  Indications, n/N (%): screening 9/31 (29); surveillance 14/31 (45); other 8/31 (26).  Location of the 235 polyps, n (%): sigmoid 125 (53), rectum 110 (47).  Histology of the 235 polyps, n (%): adenoma 38 (16); hyperplastic 188 (80); other 9 (4).  Size of the 235 polyps, n (%): ≤5mm 220 (97.8); 6-9mm 11 (4.9); ≥10mm 4 (1.8). Median size of the polyps was 3mm (range 1-20mm, interquartile range 2).  Morphology of the 235 polyps (Paris), n (%): 0-1p 7 (3.1); 0-1s 55 (24.4); 0-IIa 163 (72.4). | | | | | |
| **Endoscopist experience and training** | One endoscopist carried out the colonoscopies. The endoscopist was described as having a special interest in colonoscopy and extensive experience in NBI. No further details were provided. | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Paris classification. To describe the appearance of the polyp when using NBI, the endoscopist used established criteria (reference provided in paper13.  Hyperplastic and ‘other’ histologies were classed as nonadenomatous. Other histologies included inflammatory polyps, lymphoid follicles and normal tissue. | | | | | |
| **Sample size calculation** | Authors state that the chosen sample size was 235 distal polyps, and that this would allow 95% confidence intervals of ±3%, based on an expected true accuracy rate of 93%. Subgroups less than 235 and may be underpowered. | | | | | |
| **Results – NBI assessment of distal polyps ≤5mm (n=220)** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 27\* | | (b) 9\* | | | 36\* |
| **Index test negative** | (c) 3\* | | (d) 181\* | | | 184\* |
| **Total** | 30\* | | 190\* | | | 220 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 94.5% (95% CI, 91.5% to 97.6%) | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 90.0% | | | 73.5% to 97.9% | |
| **Clinical specificity d / (b + d)** | | 95.3% | | | 91.2% to 97.8% | |
| **PPV a / (a + b)** | | 75.0% | | | 57.8% to 87.9% | |
| **NPV d / (c + d)** | | 98.4% | | | 95.3% to 99.7% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 19.00%\* | | | 9.93% to 36.35%\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.10%\* | | | 0.04% to 0.31%\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 181.000\* | | | 46.096 to 710.717\* | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV agree with the values reported in the paper.  \* Calculated by reviewer. | | | | | | |
| **Results – NBI high confidence predictions of histology of distal polyps ≤5mm (n=201)** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 24\* | | (b) 1\* | | | 25\* |
| **Index test negative** | (c) 1\* | | (d) 175\* | | | 176\* |
| **Total** | 25\* | | 176\* | | | 201 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 99.0% (95% CI, 97.6% to 100%) – 199 of 201 (99%) polyps accurately diagnosed. | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 96.0% | | 79.7% to 99.9% | | |
| **Clinical specificity d / (b + d)** | | 99.4% | | 96.9% to 100% | | |
| **PPV a / (a + b)** | | 96.0% | | 79.7% to 99.9% | | |
| **NPV d / (c + d)** | | 99.4% | | 96.9% to 100% | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 168.96\* | | 23.89 to 1194.79\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.04\* | | 0.01 to 0.27\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 4200.000\* | | 254.269 to 69375.426\* | | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV agree with the values reported in the paper.  \* Calculated by reviewer. | | | | | | |
| **Interpretability of test** | | Not reported | | | | |
| **Inter-observer agreement** | | Not reported | | | | |
| **Intra-observer agreement** | | Not reported | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | |
| **Adverse events** | | Not reported | | | | |
| **High confidence optical diagnosis** | | Of the diminutive polyps located in the distal colon (n = 220), 201 (91.4%\*) predictions were made with high confidence.  \*% calculated by reviewer. | | | | |
| **Low confidence optical diagnosis** | | Not reported | | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | |
| **Recommended surveillance interval** | | Not reported | | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | | |
| **Number of outpatient appointments** | | Not reported | | | | |
| **Health related quality of life** | | Not reported | | | | |
| **Colorectal cancer** | | Not reported | | | | |
| **Mortality** | | Not reported | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | The majority of the patients were undergoing screening or surveillance colonoscopy. The exact indications for colonoscopy were unclear, but described by the authors as standard indications. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps received verification by histopathology (with the exception of five polyps that were not retrieved for histology) | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The pathologist who carried out the histopathology was blinded to the NBI prediction. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | 5 polyps from the total sample were not retrieved for histology and excluded from the analysis. | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated. | No |
| 11 | Were withdrawals from the study explained? | No withdrawals were reported, but there appear to be none. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant publications identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The study was conducted at one academic hospital and one endoscopist, who was experienced in NBI, carried out the colonoscopies. The findings may not therefore be generalisable to less experienced endoscopists in other settings. Although a large number of diminutive polyps were included in the study (n = 220), these came from a small number of patients (≤31 patients; exact number of patients in the diminutive polyps subgroup is unclear), which may limit the generalisability of the findings. The majority of the participants were undergoing screening or surveillance colonoscopy for standard indications (not defined). It is unclear how relevant the findings of the study are to a UK patient population. |

**Hewett et al. 2012b1**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | **Participants** | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Differentiation of hyperplastic from adenomatous polyps  (NB. Study was designed to develop and evaluate the validity of an NBI classification system – the NBI International Colorectal Endoscopic (NICE) classification system. There were 4 phases, followed by a pilot clinical evaluation of the performance of the classification system. Only the latter is relevant to this report).  **First author:** Hewett et al  **Publication year:** 2012  **Country:** USA  **Study design:** Prospective cohort  **Number of centres:** Not stated  **Funding:** Partially funded by Olympus Medical Systems Corporation (Japan).  **Competing interests:** Stated that authors are consultants to, or have received funding from,  Olympus Medical Systems  Corporation, Japan; Olympus Medical Systems Corporation; Olympus America, Inc, USA; Olympus KeyMed (Medical & Industrial Equipment) Ltd, UK; Olympus France S.A.S., and Olympus Europa Holding GmbH, Germany. | **Index test:** NBI, CF-H180AL high definition colonoscope with Exera II CLV-180 light source, CV-180 processor, and OEV-261H monitor; Olympus America, Inc). No electronic magnification used.  **Reference standard:**  Histopathology | | | | **Number of participants:**108  **Sample attrition/dropout:** of 220 enrolled patients, 108 had at least 1 polyp <1cm  **Selection of participants:** patients undergoing  routine screening, surveillance, or diagnostic colonoscopy. Received real-time endoscopic diagnosis of all consecutive polyps measuring less than 1 cm.  **Inclusion criteria for study entry:** Not stated  **Exclusion criteria for study entry:** Not stated | | **Primary outcome of study:** Not designated as primary outcomes, but reports diagnostic accuracy, sensitivity, specificity, NPV and PPV for the pilot clinical evaluation.  **Other relevant outcomes:** None  **Recruitment dates:** Not stated | |
| **Participant characteristics** | | | | | | | | |
| **Age, years, mean (SD)** | Not stated | | | | | | | |
| **Other key patient characteristics (list)** | Mean polyp size varied from 3.2mm (range 1-8), to 4.6mm (range 1-9), non adenomas and adenomas, respectively. The vast majority were ≤5mm (n=192; 81%) | | | | | | | |
| **Endoscopist experience and training** | 2 colonoscopists completed a formal standardised  training module in the use of NBI for real-time histology,  and achieved more than 90% in post-test evaluation before study  initiation. | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | The study developed and evaluated the NBI International Colorectal Endoscopic (NICE) classification system. | | | | | | | |
| **Sample size calculation** | A sample size calculation is reported for phases 1, 3, and 4, but not for the pilot clinical evaluation, which is the only part of the study relevant to this report. | | | | | | | |
| **Results –** High confidence predictions for diminutive polyps (There were 192 diminutive polyps but the number of high confidence predictions made is not reported). | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | | (a) not reported | | | | (b) not reported | | not reported |
| **Index test negative** | | (c) not reported | | | | (d) not reported | | not reported |
| **Total** | | not reported | | | | not reported | | not reported |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 88% | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 98% | | | | not reported |
| **Clinical specificity d / (b + d)** | | | | not reported | | | | not reported |
| **PPV a / (a + b)** | | | | not reported | | | | not reported |
| **NPV d / (c + d)** | | | | 95% | | | | not reported |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | not reported | | | | not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | not reported | | | | not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | not reported | | | | not reported |
| Comments: Due to the limited information reported for polyps measuring 5 mm or smaller the reviewer was unable to calculate values for the 2x2 table. | | | | | | | | |
|  | | | | | | | | |
| **Interpretability of test** | | | Not reported | | | | | |
| **Inter-observer agreement** | | | Not reported | | | | | |
| **Intra-observer agreement** | | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | | Not reported | | | | | |
| **Adverse events** | | | Not reported | | | | | |
| **High confidence optical diagnosis** | | | Of 236 polyps, diagnostic prediction was made in high confidence in 177 (75%) | | | | | |
| **Low confidence optical diagnosis** | | | Not explicitly stated, but can be assumed that 59 polyps were predicted with low confidence (177/236 were high confidence) | | | | | |
| **Number of polyps designated to be left in place** | | | Not stated | | | | | |
| **Number of polyps designated to be resected and discarded** | | | Not stated | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | Not stated | | | | | |
| **Recommended surveillance interval** | | | Not stated | | | | | |
| **Length of time to perform the colonoscopy** | | | Not stated | | | | | |
| **Number of outpatient appointments** | | | Not stated | | | | | |
| **Health related quality of life** | | | Not stated | | | | | |
| **Colorectal cancer** | | | Not stated | | | | | |
| **Mortality** | | | Not stated | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Limited information given, but patients were undergoing  routine screening, surveillance, or diagnostic colonoscopy. However, it is possible that the latter group might include patients with conditions (e.g. IBD) that are not relevant to the scope of this report. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | An independent pathologist blinded to the endoscopic prediction reported polyp histology | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated, but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Not stated if there were any withdrawals, other than of 220 enrolled patients, 108 had at least 1 polyp <1cm | Yes |

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional studies identified. |

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| --- |
| Summary reviewer’s comments |
| Limited information is given on the context of the study, but the results are based on the use of high definition NBI using the NICE criteria in a general patient population (undergoing  routine screening, surveillance, or diagnostic colonoscopy) to characterise small (<1cm, predominantly <5mm) polyps. Predictions were made with high confidence by colonoscopists with formal standardised training in the use of NBI. The study appears to have been conducted in the USA, though one of the gastroenterologists was from the UK. |

**Hoffman et al.80**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | | **Diagnostic tests** | | | **Participants** | **Outcome measures** | | |
| **Condition being diagnosed / detected:**  Screening for colorectal cancer detection of lesions & characterisation of lesions less than 5mm in the last 30cm of colon.  The overall aim of the study was to compare three imaging modalities: HD+, HD+ with i-scan and HD+ with chromoendoscopy. All three modalities were used in each patient but to overcome potential bias based on sequential examination the order that HD+ alone and HD+ with i-scan were used was randomised. The last modality was always chromoendoscopy. Only data on imaging using HD+ with i-scan are relevant to this report, data on the other two modalities (HD+ only and chromoendoscopy) have not been extracted.  Note that aspects of the study relating to detection of polyps have not been data extracted.  **First author:**  Hoffman et al.  **Publication year:** 2010  **Country:** Germany  **Study design:** Prospective cohort  **Number of centres:** 1 (endoscopic unit at the Johannes Gutenberg University of Mainz)  **Funding:** not reported  **Competing interests:** The authors disclosed no conflicts of interest. | | **Index test:** Identification of especially small lesions (less than 5mm in the last 30cm of colon) using the i-scan SE-mode & subsequent characterisation (using the i-scan p- and v-mode) of lesions to predict histology.  Used the Pentax EPKi processor providing resolution of about 1.25 megapixels per image.  The optional use of magnification was allowed after a lesion had been detected but how often this was used or what the level of magnification was is not reported.  **Reference standard:** Histopathology | | | **Number of participants:** 69  **Sample attrition/dropout:**  No participants appeared to drop out. It is not reported whether any polyps that were identified were not characterised or whether any characterised polyps were not subject to histopathology.  **Selection of participants:** Consecutive patients who fulfilled the criteria for screening colonoscopy.  **Inclusion criteria for study entry:** As above  **Exclusion criteria for study entry:** none reported | **Primary outcomes of study:**  Total amount of small lesions (<5mm) and the total amount of identified neoplastic lesions (<5mm) identified in the rectum and sigma.  (The numbers of detected lesions per patient have not data extracted because they are not relevant to this review).  **Other relevant outcomes:**  Characterisation of lesions (test performance characteristics) reported for polyps and patients.  **Recruitment dates:** Study conducted between July 2007 and January 2008. | | |
| **Participant characteristics** | | | | | | | | |
| **Age, years, mean (SD)** | | 55.9 (SD not reported) | | | | | | |
| **Other key patient characteristics (list)** | | Male n=43 (62%); Female n=26 (38%) | | | | | | |
| **Endoscopist experience and training** | | Three experienced colonoscopists performed the colonscopies. States that all were highly familiar with chromoendoscopy and HD+ Endoscopy using the Pentax EPKi processor (note HD+ not defined but is described as allowing resolution above HDTV standard. Presume is high-definition+). Discussion states examiners had a dedicated interest in colonoscopy and previous documentation of high adenoma detection rates using standard-definition colonoscopies in white light. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | All lesions were classified using the Paris classification and the surface pit pattern.  Intraepithelial neoplasia identified by histological diagnosis were divided into low and high grade using the New Vienna classification. | | | | | | |
| **Sample size calculation** | | A sample size of 20 patients was calculated. This was based the probability for error (a) set to 0.05 and a β-error set to 0.1 (reflecting a power of 0.90). It was assumed that the detection rate of conventional colonoscopy was 2 small lesions in the colorectum, and a detection rate of 7 small lesions was assumed after chromoendoscopy based on previous studies. It was assumed, in the absence of any comparative studies of HD+ and i-scan, that HD+ and i-scan would allow a 4-fold increase in the detection rate of small polyps (compared with conventional colonscopy). | | | | | | |
| **Results - analysis by polyp**  For patients investigated first with HD+ followed by i-scan (n=54). Results available only for the additional 128 lesions identified with i-scan (results presented as a per patient analysis are presented below). | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | **Total** | | |
| **Index test positive** | | not reported (a) | | | not reported (b) | not reported (a+b) | | |
| **Index test negative** | | not reported (c) | | | not reported (d) | not reported (c+d) | | |
| **Total** | | 11 (a+c) | | | 117 \*(b+d) | 128 (a+b+c+d) | | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | not reported & not possible to calculate | | | | | | |
| \* - Calculated by the reviewer | | | | | | | | |
| ***Diagnosis*** | | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | not reported & not possible to calculate | | |  | | |
| **Clinical specificity d / (b + d)** | | | not reported & not possible to calculate | | |  | | |
| **PPV a / (a + b)** | | | not reported & not possible to calculate | | |  | | |
| **NPV d / (c + d)** | | | not reported & not possible to calculate | | |  | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | not reported & not possible to calculate | | |  | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | not reported & not possible to calculate | | |  | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | not reported & not possible to calculate | | |  | | |
| Comments: Characterisation data by polyp for the 15 patients investigated firstly by i-scan followed by HD+ alone are not reported. | | | | | | | | |
| **Results - analysis by patient**  The table reporting these results is headed “Endoscopic prediction after i-scan” and from the numbers of patients given it includes all 69 patients. However, because results include a third category ‘normal mucosa’ for the index test and histopathology, 4 patients with normal mucosa by both index test and histology are omitted from the 2x2 table below. For the 54 patients investigated first by HD+ and then by i-scan it is not clear whether the analysis includes only the n=128 polyps additionally identified by i-scan or whether it also includes the n=154 polyps identified with HD+ only. | | | | | | | | |
| . | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps or normal mucosa on histopathology** | | | **Total** | |
| **Index test positive** | 9 patients (a) | | | 2 patients (b) | | | 11 patients (a+b) | |
| **Index test negative** | 2 patients (c) | | | 52 patients (41 hyperplastic & 11 normal mucosa on histology) (d) | | | 54 patients (c+d) | |
| **Total** | 11 patients (a+c) | | | 54 patients (b+d) | | | 65 patients (a+b+c+d) | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 61/65 (94%) \* | | | | | | | |
| \* - Calculated by the reviewer | | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 9/11 (82%) | | | | 48.22% to 97.72% \* |
| **Clinical specificity d / (b + d)** | | | | 52/54 (96%) | | | | 87.25% to 99.55% \* |
| **PPV a / (a + b)** | | | | 81.82% \* | | | | 48.22% to 97.72% \* |
| **NPV d / (c + d)** | | | | 96.30 % \* | | | | 87.25% to 99.55% \* |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | 22.09 \* | | | | 5.51 to 88.54 \* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | 0.19 \* | | | | 0.05 to 0.66 \* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | 117.00 \* | | | | 14.56 to 940.08 \* |
| Comments: \* - Calculated by the reviewer | | | | | | | | |
| **Interpretability of test** | | | Not commented on by the authors of the paper although results are presented which included prediction of normal mucosa as well as hyperplasia and adenoma. | | | | | |
| **Inter-observer agreement** | | | Not reported | | | | | |
| **Intra-observer agreement** | | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | | Not reported | | | | | |
| **Adverse events** | | | Not reported | | | | | |
| **High confidence optical diagnosis** | | | Not reported | | | | | |
| **Low confidence optical diagnosis** | | | Not reported | | | | | |
| **Number of polyps designated to be left in place** | | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | Not reported | | | | | |
| **Recommended surveillance interval** | | | Not reported | | | | | |
| **Length of time to perform the colonoscopy** | | | States total examination time for the last 30cm of colon did not differ significantly between the 3 groups (HD+ 4 minutes; surface enhancement with i-scan 5 minutes; chromoendoscopy with methylene blue 13 minutes). It is not clear whether these times are for detection only or include characterisation &/or polyp biopsies. | | | | | |
| **Number of outpatient appointments** | | | Not reported | | | | | |
| **Health related quality of life** | | | Not reported | | | | | |
| **Colorectal cancer** | | | Not reported | | | | | |
| **Mortality** | | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patient description limited to a statement that they fulfilled the criteria for screening colonoscopy. Mean age and number of female participants reported but no other details. | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The i-scan assessment and polyp resection occurred during the same colonoscopy | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps were resected for histopathology. No exclusions or losses were reported. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All polyps were subject to histological diagnosis. | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | One experienced pathologist who was blinded to the endoscopic findings classified the specimens. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histology had not been performed at the time of the index test | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Although results were reported for normal mucosa in addition to adenomatous and hyperplastic polyps there is no indication in the paper that this was due to any difficulty in interpreting the index test. | No |
| 11 | Were withdrawals from the study explained? | No withdrawals were reported and none appeared to have occurred. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional studies identified |

|  |
| --- |
| Summary reviewer’s comments |
| The primary outcomes of this study were total amount of small lesions (<5mm) and the total amount of identified neoplastic lesions (<5mm) identified in the rectum and sigma. Much of the reporting focuses on the detection of polyps and there is limited reporting on polyp characterisation. The three endoscopists involved in the study are described as experienced and with a particular interest in colonoscopy and therefore the results may not be applicable to less experienced endoscopists or those without a particular interest in polyp detection and characterisation. |

**Ignjatovic et al.71**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:**  Differentiation of adenomas from non-neoplastic polyps  **First author:** Ignjatovic et al  **Publication year:** 2009  **Country:** UK  **Study design:** Prospective cohort  **Number of centres:** 1 (St. Mark’s Hospital, London)  **Funding:** Leigh Family Trust, London, UK  **Competing interests:** stated none | **Index test:**  Endoscopists were  asked to predict a polyp type (hyperplastic, adenoma, carcinoma, or other) using HD white light. If unable to make an optical diagnosis, NBI was activated. The polyp was assessed in vivo with both real-time and optimised freeze frame NBI images. If colonoscopists were still unable to confidently predict polyp histology, chromoendoscopy  was used.  Narrow band imaging. High-definition (HD)  monitors and non-magnifying  Olympus CF-H260DL colonoscopes with  Lucera video processors (Olympus, Japan)  **Reference standard:**  Histopathology | | **Number of participants:** 130  **Sample attrition/dropout:**  N=48  10 patients optical diagnosis not made;  17 patients with polyp >10 mm;  15 patients polyp not retrieved;  6 patients polyp destroyed by diathermy.  **Selection of participants:** consecutive patients referred for a surveillance colonoscopy (for adenoma follow-up, but not polyposis  syndrome) or who had a positive faecal occult blood test (FOBT) at St Mark’s Hospital (London, UK)  **Inclusion criteria for study entry:**  As above  **Exclusion criteria for study entry:**  Patients with poor bowel preparation; surveillance for polyposis syndrome;  presence of an obvious cancer; polyps 10mm or larger only; absence of polyps or polyps were seen but not retrieved; no optical diagnosis made. | **Primary outcome of study:**  Accuracy of optical diagnosis  in differentiating adenomas from non-neoplastic polyps  **Other relevant outcomes:**  Number of polyps assessed with confidence;  Recommended surveillance interval; costs  **Diagnostic threshold:**  N/A  **Recruitment dates:** June 2008 to June 2009 |
| **Participant characteristics** (based on n=130 included patients. Characteristics are not available for the sub-set of patients with diminutive ≤5 mm polyps). | | | | |
| **Age, years, mean (SD)** | 63.4 (10.6) | | | |
| **Other key patient characteristics (list)**  (percentages calculated by reviewers) | Male n=87 (67%); female n=43 (33%)  Indication for colonoscopy:  FOBT n=32 (25%)  History of polyps n=68 (52%)  History of colorectal cancer n=1 (0.77%)  Family history of colorectal cancer n=14 (11%)  Change in bowel habit n=15 (12%)  First colonoscopy n=60 (46%)  Previous colonoscopy n=70 (54%)  Total number of polyps detected n= 363 (overall sample of polyps)  Polyps ≤5 mm n= 296  Polyps 6 – 9 mm n= 67 | | | |
| **Endoscopist experience and training** | Colonoscopists referred to as experts or non-experts. Procedures were done by four colonoscopists: two experts who had previously done more than 10,000 colonoscopies with experience of NBI in more than  1000 cases, one trainee (<500 colonoscopies, <50 NBI colonoscopies), and one specialist nurse (>3000 colonoscopies, <10 NBI colonoscopies). All four colonoscopists were familiar with vascular pattern intensity (VPI) classification, and the non-experts completed a training session on use of NBI in characterising polyps, using a library of images collected as part of a previous study.  Expert colonoscopists mainly examined patients were high risk and FOBT positive, as part of the national bowel-cancer screening programme. Non experts did routine surveillance colonoscopies.  Non-expert colonoscopists assessed 104 polyps in 64 patients and experts assessed 259 polyps in 66 patients, reflecting the fact that experts examined patients who were more likely to have a greater number of polyps. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Polyp histology was classified according to the VPI criteria. The location, size, and shape of polyps was recorded with the Paris classification system. | | | |
| **Sample size calculation** | Total of 278 polyps needed to be prospectively assessed, assuming an accuracy for optical diagnosis of 93% (± 3%) | | | |
| **Results: sub-sample of polyps** ≤ **5 mm** | | | | |
|  | **Number of neoplastic polyps on histopathology** | | **Number of non- neoplastic polyps on histopathology** | **Total** |
| **Index test positive** | (a) 144 | | (b) 7 | 151 |
| **Index test negative** | (c) 11 | | (d) 51 | 62 |
| **Total** | 155 | | 58 | 213 |
| **Accuracy of index test** ([a+d]/[a+b+c+d]) | 195/213 (92%) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 92.90% | | 87.66% to 96.40% |
| **Clinical specificity d / (b + d)** | | 87.93 % | | 76.70% to 95.01% |
| **PPV a / (a + b)** | | 95.36%\* | | 90.68% to 98.12% |
| **NPV d / (c + d)** | | 82.26 %\* | | 70.47% to 90.80% |
| **Positive likelihood ratio [sensitivity/(1- specificity)]** | | 7.70\* | | 3.84 to 15.44 |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.08\* | | 0.05 to 0.14 |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 95.38\* | | 35.08 to 259.27 |
| Comments:   * 278 polyps had both a high confidence optical and histopathological diagnosis (overall sample of polyps). For the sub-sample of polyps ≤5 mm this figure was 213. * Diagnostic accuracy estimates (sensitivity, specificity etc) are given for the overall sample of polyps (i.e. irrespective of polyp size), and stratified by whether an expert or non-expert performed the colonoscopy. These data are not extracted here as they include polyp sizes larger than the scope of this assessment. * Sensitivity and specificity are similar for the overall sample and the diminutive (≤5 mm) polyp sub-group. Expert colonoscopists were more accurate than non-experts in optical diagnosis of adenomas (p=0.04) * 68 of 198 adenomas and 20 of 62 non-neoplastic lesions were correctly diagnosed using white light endoscopy alone (in the overall sample of polyps). The remaining polyps were diagnosed by a combination of white light and NBI, except for one adenoma and 2 hyperplastic lesions for which chromoendoscopy was also used. * Sub-group analyses were conducted for polyp size (6-9mm vs 5mm) and for endoscopists’ experience. It is not explicitly stated whether these were pre-defined sub-groups.   \* calculated by the reviewer | | | | |
| **Interpretability of test** | | Not stated | | |
| **Inter-observer agreement** | | Not reported | | |
| **Intra-observer agreement** | | Not reported | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | |
| **Adverse events** | | Not reported | | |
| **High confidence optical diagnosis** | | N=323/363 | | |
| **Low confidence optical diagnosisa** | | N=37/363 | | |
| **Low confidence polyps ≤ 5 mm** | | N=22/293 (8%) | | |
| **Low confidence polyps 6 – 9 mm** | | N=15/67 (22%) | | |
| **No diagnosis made** | | N=3/363 (all ≤ 5mm) | | |
| **Number of polyps left in placeb** | | 33/323 (high confidence decision, for overall sample of polyps)  All were hyperplastic polyps and located in the sigmoid colon or the rectum | | |
| **Number of polyps resected and discardedb** | | 290/323 (high confidence decision, for overall sample of polyps) | | |
| **Number of polyps resected and sent for histological examination** | | 22/293 (8%) (sub-sample of polyps ≤ 5 mm) | | |
| **Recommended surveillance interval** | | Given in 82/130 patients. Surveillance intervals based on histopathology and optical diagnosis were the same for 80/82 patients (98%) using BSG guidelines. Two patients had a longer interval recommended after histopathology. There was no difference between experts and non-experts in the accuracy of surveillance interval prediction (36 of 37 [97%] *vs* 44 of 45 [98%], p=1.00) | | |
| **Total cost of histopathology (n=363 polyps)c** | | £7623 | | |
| **Total cost for optical diagnosis (n=323 polyps)c** | | £840 | | |
| **Total cost of follow-up appointments histopathologyd** | | £10,400 | | |
| **Total cost of follow-up appointments optical diagnosisd** | | £3840 | | |
| **Length of time to perform the colonoscopy** | | Not stated | | |
| **Number of outpatient appointments** | | Not stated | | |
| **Health related quality of life** | | Not stated | | |
| **Colorectal cancer** | | Not stated | | |
| **Mortality** | | Not stated | | |

a = endoscopists chose to resect and send for elective histopathology

b= for the purposes of the study all polyps were resected and submitted for histopathology

c = Cost per polyp of £21 (UK National Tariff 2008-09 Department of Health)

d = £80 each (UK National Tariff 2008-09 Department of Health)

N/A = Not applicable

HD = High definition

FOBT = Faecal occult blood test

VPI = Vascular Pattern Intensity

BSG = British Society of Gastroenterology

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Two groups of patients were recruited – those indicated for colonoscopy based on surveillance, and those referred from bowel screening (positive FOBT). These are relevant to the scope of the appraisal. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The aim was to resect and submit all polyps for histopathology. Diagnostic accuracy results were reported for the sample of 278 polyps which had both an optical and histopathological diagnosis. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Experienced gastrointestinal  histopathologists, who were blinded to endoscopic images and optical predictions, classified all specimens according to WHO guidelines | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated, but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Of 130 patients initially included, 48 appear to have been excluded from the analysis for a variety of reasons which are provided (e.g. no optical diagnosis was made; patients had polyps sized ≥10mm in addition to polyps ≤10mm; polyps not retrieved; polyps destroyed by diathermy). | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes |

|  |
| --- |
| Summary reviewer’s comments |
| This was a UK study and participants had been referred for colonoscopy following a positive FOBT or for surveillance (adenoma follow up but not polyposis syndromes). These participants are likely to be representative of others in the UK. Colonoscopists were experts (n=2) or non-experts (n=2) and although results were provided separately for all polyps by colonoscopist expertise they were not provided separately for diminutive polyps. |

**Ikematsu et al.72**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | **Outcome measures** |
| **Condition being diagnosed / detected:**  Differentiation between adenomatous and hyperplastic polyps.  **First author:** Ikematsu  **Publication year:** 2015  **Country:** Japan  **Study design:** prospective cohort  **Number of centres:**  Two (National Cancer Center East Hospital and National Cancer Center Hospital).  **Funding:** not reported  **Competing interests:** Stated that the 10 authors had no conflicts of interest or financial ties to disclose. | **Index test:**  NBI without magnification to differentiate between adenomatous or hyperplastic polyps in real time. Endoscopists assigned a level of confidence (either high or low) to their prediction of polyp histology.  EVIS LUCERA ELITE, CV-290 (Olympus, Optical Co. Ltd, Tokyo, Japan) with a dual-focus colonoscope (CF-HQ290I)  **Reference standard:**  Histopathological examination.  Note that the study also included white-light imaging and NBI with dual-focus (magnification approximately 72-fold) but these data do not meet the inclusion criteria for this review so have not been extracted. | | **Number of participants:** 37 (100 polyps, 72 polyps were ≤ 5mm in size)  **Sample attrition/dropout:**  None reported  **Selection of participants:**  Consecutive patients who underwent screening colonoscopy  **Inclusion criteria for study entry:**  Not reported  **Exclusion criteria for study entry:** patients with polyps >10 mm, with lesions previously evaluated by histology or colonoscopy, and patients with invasive carcinoma. Patients with inflammatory bowel disease or familial adenomatous polyposis were also excluded. | | **Primary outcome of study:**  Accuracy, sensitivity, specificity, negative predictive value, positive predictive value, level of confidence in each modality to differentiate between adenomatous and hyperplastic lesions and predict pathological findings (only NBI data extracted).  **Secondary outcome measure**: ability of each modality to differentiate lesions based on their size (≤5 mm and 6-10mm) (only NBI data extracted).  **Recruitment dates:** July to December 2013 |
| **Participant characteristics** | | | | | |
| **Age, years, mean (SD)** | 66.9 (range 39 to 82 years) | | | | |
| **Other key patient characteristics** | Gender M/F 28/9 (ratio M:F 3.1:1)  Bowel preparation: Excellent n=23; Good n=13; Fair n=1; Poor n=0  Paris classification type: 0-Is n=18; 0-IIa n=82  Size of resected polyps (not stated but presume mean value): 4.6 mm (range 2-10mm)  Location of polyps: right colon n=51, left colon n=40; rectum n=9.  Histological findings: tubular adenoma with low-grade dysplasia n=74; tubular adenoma with high-grade dysplasia n=2; hyperplastic polyp n=24 | | | | |
| **Endoscopist experience and training** | Seven endoscopists participated who had each performed >1000 colonoscopies and >500 NBI colonoscopies. No information provided regarding any endoscopist training. | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | The Paris classification was used to describe macroscopic appearance of the polyps.  Histopathological results were determined according to WHO criteria. | | | | |
| **Sample size calculation** | Not reported | | | | |
| **Results: for the sub-group of polyps ≤5mm in size** | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | a = 50 \* | | b = 3 \* | | a+b= 53\* |
| **Index test negative** | c = 4 \* | | d = 15\* | | c+d = 19\* |
| **Total** | a+c = 54\* | | b+d =18\* | | 72 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90.3% | | | | |
| \* = calculated by reviewer. The reviewer calculated values for the 2x2 table produce almost identical sensitivity, specificity, positive predictive, and negative predictive value to those reported in the paper. | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 92.6 | | 82.11% to 97.94% \* | |
| **Clinical specificity d / (b + d)** | | 83.3 | | 58.58% to 96.42% \* | |
| **PPV a / (a + b)** | | 94.3 | | 84.34% to 98.82% \* | |
| **NPV d / (c + d)** | | 78.9 | | 54.43% to 93.95% \* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.56 \* | | 1.97 to 15.65 \* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.09 \* | | 0.03 to 0.23 \* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 62.5 \* | | 12.56 to 310.90 \* | |
| **Interpretability of test** | | Not reported | | | |
| **Inter-observer agreement** | | Not reported | | | |
| **Intra-observer agreement** | | Not reported | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | |
| **Adverse events** | | Not reported | | | |
| **High confidence optical diagnosis** | | For polyps ≤5mm in size 53/72 (73.6%) of predictions were made with high confidence. | | | |
| **Low confidence optical diagnosis** | | Not reported | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | |
| **Recommended surveillance interval** | | Not reported | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | |
| **Number of outpatient appointments** | | Not reported | | | |
| **Health related quality of life** | | Not reported | | | |
| **Colorectal cancer** | | Not reported | | | |
| **Mortality** | | Not reported | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Japanese patients attending for screening colonoscopy. No other inclusion criteria reported | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered the gold standard | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Histopathological diagnoses were performed by experienced gastrointestinal pathologists who were blinded to the prediction made during NBI colonoscopy. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histology had not yet been performed at the time of the index test. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | No evidence of uninterpretable test results | No |
| 11 | Were withdrawals from the study explained? | No evidence of withdrawals from study | Yes |

yes / no / unclear; n/a - not applicable

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional studies were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| It is not clear how representative these Japanese patients are to the UK population undergoing colonoscopy, in part because few details were provided about the included patients. The endoscopists involved were all experienced in the use of the technology so the results might not be applicable to those new to NBI. |

**Iwatate et al.4**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | **Participants** | | | | | **Outcome measures** | | | |
| **Condition being diagnosed / detected:** The impact of high magnifying endoscopy (ME) vs non-magnification endoscopy (NME) NBI-based optical diagnosis of colorectal polyps on rates of high confidence assessment when differentiating neoplastic and non-neoplastic polyps.  **First author:** Iwatate et al.  **Publication year:** 2015  **Country:** Japan  **Study design:** Prospective study  **Number of centres:** 1 (non-academic)  **Funding:** Not stated  **Competing interests:** None | **Index test:** NBI. Magnifying colonoscopes (H260AZI; maximum, ×80 optical zoom;  Olympus, Tokyo, Japan) with LUCERA video processors (Olympus) and high definition monitors.  All polyps detected by white light imaging during colonoscopy were washed intensively and examined in two stages, first by NBI-NME and subsequently by NBI-ME (the later data was not extracted). The polyp size was estimated with biopsy forceps (2.2 mm closed; EndoJaw, Olympus) or polypectomy snare (10mm open; Dragonare S, Xemex, Tokyo, Japan).  **Reference standard:** Histopathology | | | **Number of participants:** 124  **Sample attrition/dropout:** no dropouts reported  **Selection of participants:**  consecutive adult patients scheduled for a high magnifying (maximum, ×80) colonoscope colonoscopy  **Inclusion criteria for study entry:** adults aged <70 years scheduled to undergo colonoscopy with a magnifying colonoscope  **Exclusion criteria for study entry:**   * polyps ≥11 mm * multiple (> 10) polyps (for ethical reasons, given the longer examination time) * without polyps or whose polyp histopathology had not been evaluated * poor bowel preparation, melanosis, or a history of inflammatory bowel disease, hereditary polyposis syndrome, or Lynch syndrome. | | | | | **Primary outcome of study:** not stated  **Other relevant outcomes:**  sensitivity, specificity, accuracy, PPV, NPV;  Sensitivity, specificity, accuracy, PPV and NPV for high confidence optical diagnosis by specialists in colonoscopy (SCs) and general endoscopists (GEs); Effect of NBI-ME on level of confidence with accuracy by NBI-NME (not data extracted).  **Recruitment dates:** April and  August 2012 | | | |
| **Participant characteristics (all n=124, 248 polyps)** | | | | | | | | | | | | |
| **Age, years, mean (SD)** | | 56.4 (8.7) | | | | | | | | | | |
| **Other key patient characteristics** | | Male, %: 58 | | | | | | | | | | |
|  | | Polyps | | | | | | | | | | |
|  | | 1 –5mm/6– 9mm, n: 210/38 | | | | | | | | | | |
|  | | Mean size, mm (SD): 3.7 (1.7) | | | | | | | | | | |
|  | | Location, right side/left side, n: 128/120 | | | | | | | | | | |
|  | | Shape, protruded/flat/depressed, n: 80/166/2 | | | | | | | | | | |
|  | | Histopathology 1 –5mm (6-9 mm not data extracted), n | | | | | | | | | | |
|  | | Hyperplastic polyp: 68 | | | | | | | | | | |
|  | | Sessile serrated adenoma/polyp: 1 | | | | | | | | | | |
|  | | Low grade adenoma: 141 | | | | | | | | | | |
|  | | High grade adenoma: 0 | | | | | | | | | | |
|  | | Deep submucosal invasive carcinoma: 0 | | | | | | | | | | |
| **Endoscopist experience and training** | | 5 endoscopists: 2 specialists in colonoscopy (SCs), with extensive experience in magnifying colonoscopy with NBI (>1000 cases) and 3 general endoscopists (GEs), with limited experience in magnifying colonoscopy with NBI (≤1000 cases). All 5 endoscopists were familiar with the NBI international colorectal endoscopic (NICE) classification. | | | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | Paris classification for location, size, and shape.  Polyp type: NICE classification (1. non-neoplastic lesion, 2. adenoma, 3. deep submucosal invasive carcinoma). Endoscopists had to assign their level of confidence (high or low) to the prediction.  Histopathological classification: World Health Organization  Classification (WHO) classification.  Neoplastic lesions: adenoma, traditional serrated adenoma, or carcinoma;  Others, including hyperplastic polyps: non-neoplastic lesions.  Sessile serrated adenomas/polyps: non-neoplastic lesions (stated that this was due to the endoscopic criteria to distinguish sessile serrated adenomas/polyps from hyperplastic polyps or a pathologic gold standard for diagnosis has not been fully established). | | | | | | | | | | |
| **Sample size calculation** | | To detect a significant difference between a high confidence rate of an 90% rate with a two-sided 5% significance level and 80% power with McNemar’s test for the NBI with NME and NBI-ME, a sample size of 250 consecutive polyps was required –248 polyps were identified in the total sample of 124 patients. | | | | | | | | | | |
| **Results** | | | | | | | | | | | | |
| **NBI-NME 1–5 mmm subgroup: All** | | **Adenomatous polyps on histopathology** | | | | **Hyperplastic polyps on histopathology** | | | | | **Total** | |
| **Index test positive** | | (a) 123 | | | | (b) 25\* | | | | | 148 | |
| **Index test negative** | | (c) 18\* | | | | (d) 44 | | | | | 62 | |
| **Total** | | 141 | | | | 69 | | | | | 210 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 79.5% (167/210) (CI not reported and not calculated by reviewer) | | | | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 87.2% | | | | 80.58% to 92.26%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | 63.8% | | | | 51.31% to 75.01%\* | | |
| **PPV a / (a + b)** | | | | | | 83.1% | | | | 76.08% to 88.76%\* | | |
| **NPV d / (c + d)** | | | | | | 71.0% | | | | 58.05% to 81.80%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 2.41\* | | | | 1.75 to 3.31\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.20\* | | | | 0.13 to 0.32\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 12.027\* | | | | 5.991 to 24.143\* | | |
| Comments: \* Calculated by reviewer.  Calculations agree with values reported in paper, (although approximation of rounding differs). | | | | | | | | | | | | |
| **NBI-NME 1–5 mmm subgroup: High confidence** | | **Adenomatous polyps on histopathology** | | | | **Hyperplastic polyps on histopathology** | | | | | **Total** | |
| **Index test positive** | | (a) 107 | | | | (b) 17\* | | | | | 124 | |
| **Index test negative** | | (c) 8\* | | | | (d) 35 | | | | | 43 | |
| **Total** | | 115 | | | | 52 | | | | | 167 | |
| **Accuracy ([a+d]/[a+b+c+d])** | | 85.0% (142/167) (CI not reported and not calculated by reviewer) | | | | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 93.0% | | | | 86.75% to 96.95%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | 67.3% | | | | 52.89% to 79.67%\* | | |
| **PPV a / (a + b)** | | | | | | 86.3% | | | | 78.96% to 91.81%\* | | |
| **NPV d / (c + d)** | | | | | | 81.4% | | | | 66.60% to 91.61%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 2.85\* | | | | 1.92 to 4.22\* | | |
| **Negative likelihood ratio [(1-sensitivity)/ specificity]** | | | | | | 0.10\* | | | | 0.05 to 0.21\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 27.537\* | | | | 10.942 to 69.301\* | | |
|  | | | | | | | | | | | | |
| **NBI-NME 1–5 mmm subgroup: Low confidence** | | **Adenomatous polyps on histopathology** | | | | **Hyperplastic polyps on histopathology** | | | | | **Total** | |
| **Index test positive** | | (a) 16 | | | | (b) 8\* | | | | | 24 | |
| **Index test negative** | | (c) 10 | | | | (d) 9 | | | | | 19 | |
| **Total** | | 26 | | | | 17 | | | | | 43 | |
| **Accuracy ([a+d]/[a+b+c+d])** | | 58.1% (25/43) (CI not reported and not calculated by reviewer) | | | | | | | | | | |
| **Comments:** | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 61.5% | | | | 40.57% to 79.77%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | 52.9% | | | | 27.81% to 77.02%\* | | |
| **PPV a / (a + b)** | | | | | | 66.7% | | | | 44.68% to 84.37%\* | | |
| **NPV d / (c + d)** | | | | | | 47.4% | | | | 24.45% to 71.14%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 1.31 | | | | 0.73 to 2.36 | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.73 | | | | 0.38 to 1.41 | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 1.800 | | | | 0.522 to 6.204 | | |
|  | | | | | | | | | | | | |
| **Diagnostic accuracy rates of SCs for high confidence predictions when using NBI-NME: 1 -5 mm subgroup** | | | **Adenomatous polyps on histopathology** | | | | | **Hyperplastic polyps on histopathology** | | | | **Total** |
| **Index test positive** | | | (a) 29 | | | | | (b) 3\* | | | | 32 |
| **Index test negative** | | | (c) 2\* | | | | | (d) 20 | | | | 22 |
| **Total** | | | 31 | | | | | 23 | | | | 54 |
| **Accuracy ([a+d]/[a+b+c+d])** | | | 90.7% (n/N: 49/54) | | | | | | | | | |
| ***Diagnosis*** | | | | | | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | | 93.5% | | | 78.58% to 99.21%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | | 87.0%1 | | | 66.41% to 97.22%\* | | |
| **PPV a / (a + b)** | | | | | | | 90.6% | | | 74.98% to 98.02%\* | | |
| **NPV d / (c + d)** | | | | | | | 90.9% | | | 70.84% to 98.88%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | | 7.17\* | | | 2.49 to 20.69\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | | 0.07\* | | | 0.02 to 0.29\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | | 96.667\* | | | 14.784 to 632.049\* | | |
| Comments: \* calculated by reviewer. The reviewer calculated values for the 2x2 table produce almost identical sensitivity, specificity, PPV and NPV values to those reported in the paper.  1 The differences between the specificity rates for the SC and the GE group were significant p=0.007. | | | | | | | | | | | | |
| **Diagnostic accuracy rates of GEs for high confidence predictions when using NBI-NME: 1 -5 mm subgroup** | | | **Adenomatous polyps on histopathology** | | | | | **Hyperplastic polyps on histopathology** | | | | **Total** |
| **Index test positive** | | | (a) 78 | | | | | (b) 14\* | | | | 92 |
| **Index test negative** | | | (c) 6\* | | | | | (d) 15 | | | | 21 |
| **Total** | | | 84 | | | | | 29 | | | | 113 |
| **Accuracy ([a+d]/[a+b+c+d])** | | | 82.3% (n/N: 93/113) | | | | | | | | | |
| ***Diagnosis*** | | | | | | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | | 92.9% | | | 85.10% to 97.33%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | | 51.7%1 | | | 32.53% to 70.55%\* | | |
| **PPV a / (a + b)** | | | | | | | 84.8% | | | 75.79% to 91.42%\* | | |
| **NPV d / (c + d)** | | | | | | | 71.4% | | | 47.82% to 88.72%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | | 1.92 \* | | | 1.31 to 2.82\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | | 0.14 \* | | | 0.06 to 0.32\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | | 13.929\* | | | 4.615 to 42.034\* | | |
| Comments: \* calculated by reviewer. The reviewer calculated values for the 2x2 table produce identical sensitivity, specificity, PPV and NPV values to those reported in the paper.  1 The differences between the specificity rates for the SC and the GE group were significant p=0.007. | | | | | | | | | | | | |
| **Interpretability of test** | | | | | Not reported | | | | | | | |
| **Inter-observer agreement** | | | | | Not reported | | | | | | | |
| **Intra-observer agreement** | | | | | Not reported | | | | | | | |
| **Test acceptability (patients / clinicians)** | | | | | Not reported | | | | | | | |
| **Adverse events** | | | | | Not reported | | | | | | | |
| **High confidence optical diagnosis** | | | | | Endoscopists made a prediction with high confidence when they were 90% certain of the diagnosis (Hewett et al., 2012, reference provided in the paper) and the diagnosis at each stage was recorded by an independent observer, who did not allow the prediction to be changed at subsequent steps.  Rates of high confidence optical diagnosis with NBI-NME for 1–5 mm subgroup, % (n/N): 79.5 (167/210).  Effect of NBI-ME on level of confidence with accuracy by NBI-NME: accuracy of high confidence level for this outcome not data extracted. | | | | | | | |
| **Low confidence optical diagnosis** | | | | | Effect of NBI-ME on level of confidence with accuracy by NBI-NME: accuracy of low confidence level not data extracted.  Rates of low confidence optical diagnosis with NBI-NME for 1-5mm subgroup, % (n/N) 20.5\* (43/210)  \* calculated by reviewer | | | | | | | |
| **Number of polyps designated to be left in place** | | | | | Not reported | | | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | | Not reported | | | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | | Not reported | | | | | | | |
| **Recommended surveillance interval** | | | | | Not reported | | | | | | | |
| **Length of time to perform the colonoscopy** | | | | | Not reported | | | | | | | |
| **Number of outpatient appointments** | | | | | Not reported | | | | | | | |
| **Health related quality of life** | | | | | Not reported | | | | | | | |
| **Colorectal cancer** | | | | | Not reported | | | | | | | |
| **Mortality** | | | | | Not reported | | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients aged 70years or less scheduled to undergo a magnifying colonoscopy. Exact indication for colonoscopy was not provided | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps in the prospective study were resected or biopsied for histopathologic evaluation as the reference standard. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | An experienced gastrointestinal histopathologist blinded to the endoscopic diagnosis classified all specimens according to the World Health Organization  Classification. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | 2 patients with ‘unevaluable material’ were excluded. | Yes |
| 11 | Were withdrawals from the study explained? | While not specifically stated, there appear to have been no withdrawals. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant reverences were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The population sample was based on patients from Japan and it is unclear how representative the population is of the patient population in the UK, and how similar endoscopists’s training is compared to training received in the NHS. Study was performed in a single centre, so the results may not be applicable to a wider range of settings. Patients were scheduled to undergo colonoscopy with a magnifying colonoscope, but exact indication for colonoscopy was not provided. Therefore, it is unclear how relevant the patient population in this study is to the population of interest in this appraisal. |

**Kaltenbach et al.5**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | | | **Outcome measures** |
| **Condition being diagnosed / detected:**  Differentiating neoplastic and non-neoplastic diminutive colorectal polyps.  **First author:** Kaltenbach et al. & McGill et al. All data without a reference number is extracted from Kaltenbach. Data extracted from McGill is clearly indicated by inclusion of the reference number and/or ‘McGill paper’.  **Publication year:** 2015 (both Kaltenbach and McGill)  **Country:** USA  **Study design:** RCT (with one relevant arm: NBI standard view 30X colonoscope)  **Number of centres:** 3  **Funding:**  Study was partially funded by Olympus Medical America. Other funding sources not stated.  **Competing interests:** Three of the authors have received research funding from Olympus Medical America and are consultants for Olympus Medical Systems Corporation. There were no other conflicts. | **Index test:**  NBI standard-focus (30X) colonoscope (CFH180AL, EVIS Exera II).  High definition (HD) monitors were used (OEV-261H).  HD standard-view white light was initially used to examine a polyp. When a polyp was found, optical diagnosis was made using the NBI mode.  Participants could also be randomised to NBI dual-focus (65X) colonoscopy in this RCT: results from this arm have not been data extracted, as magnification was used.  **Reference standard:**  Histopathology | | **Number of participants:**  558 participants enrolled and randomised into the study (total sample); 281 participants included in the standard-focus arm and included in the analysis (missing data were imputed for two participants).  **Sample attrition/dropout:**  2 patients did not have a complete colonoscopy due to poor bowel preparation quality or stricture in the standard-view arm. Missing data were imputed for these participants.  **Selection of participants:**  Consecutively recruited patients who were undergoing routine colonoscopy.5 McGill paper,73 states that patients were undergoing colonoscopy for screening, surveillance or symptoms.  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  Referred for polypectomy; colitis; personal or family history of polyposis or hereditary colorectal cancer syndrome, or coagulopathy / thrombocytopenia.5 McGill paper states that patients were also excluded if they needed an emergent endoscopy, had a known existing polyp, or had poor or inadequate bowel preparation.73 | | | | **Primary outcome of study:**  Proportion of accurate high-confidence optical diagnoses of neoplastic and non-neoplastic diminutive colorectal polyps.5  McGill paper73 states that the main endpoints were NPV (for high confidence diminutive polyps only) and surveillance interval agreement between optical diagnosis and histopathology (overall and by individual endoscopist).  **Other relevant outcomes:**  Accuracy, sensitivity, specificity, PPV and NPV. Agreement in assignment of surveillance intervals between optical diagnosis and histopathology.  Adverse events. Procedure and inspection time.  **Recruitment dates:** March 2011 to May 2012 |
| **Participant characteristics** | | | | | | | |
| **Age, years, mean (SD)** | Standard-view arm, mean +/- SD years (range): 62.4 +/- 8.7 (31-90) | | | | | | |
| **Other key patient characteristics** | Standard-view arm, male, n/N (%): 269/281 (95.7%).  Standard-view arm, colonoscopy indication, n (%): screening, 106 (37.7%); surveillance, 123 (43.8%); symptoms (anaemia, intermittent rectal bleeding, change in stool pattern, abdominal pain, weight loss), 52 (18.5%).  445 polyps from 281 patients were assessed in the standard-view arm. 3 polyps were not retrieved for histopathological examination, resulting in a sample of 442 polyps. Of the 442 polyps, 252 (57.0%\*) were neoplastic and 190 (43.0%\*) were non-neoplastic. \*Calculated by reviewer. Exact pathology (i.e. cancer, high grade dysplasia, villous adenoma, hyperplastic, other) is also provided in the paper, but not data extracted.  Polyp shape: of the 442 polyps, 381 were sessile, 59 flat and 2 depressed.  Polyp location of the 442 polyps, n: caecum, 30; ascending, 81; hepatic flexure, 10; transverse, 99; splenic flexure, 1; descending, 40; sigmoid, 117; and, rectum, 64.  McGill paper73 reports that of the 558 patients analysed, 219 (39.2%\*) patients had diminutive polyps, 210 (37.6%\*) had diminutive and other polyps, and 129 (23.1%) had no polyps. (\*%s calculated by reviewer.) Overall, 975 diminutive polyps were assessed, of which 445 were diagnosed with high confidence in the standard-view arm (endoscopists made a high confidence assessment for 72.6% of the polyps assessed in the standard view arm).  Mean (SD, range) polyp size in standard-view arm, mm, by histopathology: neoplasia histopathology, 3.37 (1.13, 1-5); non-neoplasia histopathology, 2.99 (1.16, 1-5). | | | | | | |
| **Endoscopist experience and training** | Five endoscopists performed the colonoscopies. Before the study started, all took part in training in optical diagnosis of colorectal polyp histology using a Learning Management System, exceeding 90% accuracy. It is stated on p. 1570 that “They used the NBI International Colorectal Endoscopic (NICE) classification”. No other information is provided about the endoscopists’ training or experience in the Kaltenbach paper.5  In the McGill paper,73 it is stated that the five endoscopists took part in a computer-based training module, based on the NICE criteria, and (as stated above) had to meet a minimum accuracy of 90%. They then carried out 10 real-time colonoscopies. The endoscopists’ histology predictions were compared with histopathology results. The endoscopists repeated the training module mid-way through the study. The endoscopists had 3-15 years clinical practice experience. Each endoscopist had annually performed between 500 – 1200 colonoscopies. All were based in an academic setting and all were familiar with NBI. Three were experts in the use of NBI. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | During optical diagnosis, the polyps were classified using the NBI International Colorectal Endoscopic (NICE) classification. The Paris classification was used to estimate polyp size and morphology.  During histopathology, the polyps were defined as an adenoma or hyperplastic using the World Health Organisation (WHO) criteria. | | | | | | |
| **Sample size calculation** | It was assumed that 90% of polyps would be diagnosed with high confidence when using near-focus and 80% when using standard-focus. Based on the authors’ previously collected data, they assumed a 97% caecal intubation rate, 5% poor bowel preparation, and that 60% of patients would have a colorectal lesion with a mean neoplasm of 0.85. This resulted in an estimated sample size needed of 279 patients in each study arm to provide a power of 80% with a two-sided level of 0.05 to detect a difference between the study arms in the proportions of accurate high-confidence optical diagnoses.5  The reported sample size calculation in the McGill paper73 differs to that reported in the Kaltenbach paper5 above. It was calculated that a sample size of 219 polyps in each study arm was needed to provide a power of 80% (at a two-sided alpha level of 0.05). This was based on the assumption, based on previous studies, that using the standard view and dual-focus NBI colonoscopes would each provide a 93% accuracy, with the standard view colonoscope and the dual-focus colonoscope predicting 80% and 90% of polyps with high confidence, respectively. | | | | | | |
| **Results - Standard-view NBI, high confidence diagnoses of all diminutive polyps (n = 323ǂ)** | | | | | | | |
|  | **Adenomatous\* polyps on histopathology** | | **Hyperplastic\*\* polyps on histopathology** | | | | **Total** |
| **Index test positive** | (a) 178\*\*\* | | (b) 33\*\*\* | | | | 211\*\*\* |
| **Index test negative** | (c) 9\*\*\* | | (d) 103\*\*\* | | | | 112\*\*\* |
| **Total** | 187\*\*\* | | 136\*\*\* | | | | 323 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 87.0% (95% CI, 82.8% to 90.5%) | | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | 95.2% | | 90.8% to 97.6% | | | |
| **Clinical specificity d / (b + d)** | | 75.7% | | 67.5% to 82.5% | | | |
| **PPV a / (a + b)** | | 84.4% | | 78.7% to 89.0% | | | |
| **NPV d / (c + d)** | | 92.0% | | 85.3% to 96.3% | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 3.92\*\*\* | | 2.91 to 5.29\*\*\* | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.06\*\*\* | | 0.03 to 0.12\*\*\* | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 61.731\*\*\* | | 28.412 to 134.121\*\*\* | | | |
| Reviewer’s calculations of sensitivity, specificity, PPV and NPV agree with the values reported in the paper, but the reviewer’s calculations resulted in slightly differing 95% CIs: sensitivity, 95.19% (95% CIs, 91.06% to 97.78%; specificity, 75.74% (95% CIs, 67.64% to 82.67%); PPV, 84.36% (95% CIs, 78.74% to 88.98%); NPV, 91.96% (95% CIs, 85.29% to 96.26%).  \* Neoplastic polyps, defined as tubular adenoma, villous adenoma, high-grade dysplasia or cancer.  \*\* Non-neoplastic polyps, defined as hyperplastic, sessile serrated adenoma/polyp or inflammatory.  \*\*\* Calculated by reviewer.  ǂ Reported to be n = 445 in McGill paper73 – please see note below. | | | | | | | |
| **Results – Standard-view NBI, high confidence diagnoses of diminutive polyps located in the rectum (n = 46)** | | | | | | | |
|  | **Adenomatous\* polyps on histopathology** | | **Hyperplastic\*\* polyps on histopathology** | | | | **Total** |
| **Index test positive** | (a) 7\*\*\* | | (b) 7\*\*\* | | | | 14\*\*\* |
| **Index test negative** | (c) 2\*\*\* | | (d) 30\*\*\* | | | | 32\*\*\* |
| **Total** | 9\*\*\* | | 37\*\*\* | | | | 46 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 80.4% (95% CI, 66.1% to 90.6%) | | | | | | |
| ***Diagnosis*** | | **Value** | | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 77.8% | | | | 40.0% to 97.2% | |
| **Clinical specificity d / (b + d)** | | 81.1% | | | | 64.8% to 92.0% | |
| **PPV a / (a + b)** | | 50.0% | | | | 23.0% to 77.0% | |
| **NPV d / (c + d)** | | 93.8% | | | | 79.2% to 99.2% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.11\*\*\* | | | | 1.94 to 8.73\*\*\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.27\*\*\* | | | | 0.08 to 0.94\*\*\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 15.000\*\*\* | | | | 2.545 to 88.397\*\*\* | |
| Comments: Paper also reports that for a subgroup of diminutive polyps in the **rectosigmoid**, the NPV was 93.6% (95% CI, 85.7% to 97.9%) when using standard-view.  Reviewer’s calculations of values and 95% CIs match those reported in the paper.  \* Neoplastic polyps defined as tubular adenoma, villous adenoma, high-grade dysplasia or cancer.  \*\* Non-neoplastic defined as hyperplastic, sessile serrated adenoma/polyp or inflammatory.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results - Standard-view NBI, high confidence diagnoses of diminutive polyps located in the right colon (n = 155)** | | | | | | | |
|  | **Adenomatous\* polyps on histopathology** | | **Hyperplastic\*\* polyps on histopathology** | | | | **Total** |
| **Index test positive** | (a) 107\*\*\* | | (b) 17\*\*\* | | | | 124\*\*\* |
| **Index test negative** | (c) 4\*\*\* | | (d) 27\*\*\* | | | | 31\*\*\* |
| **Total** | 111\*\*\* | | 44\*\*\* | | | | 155 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 86.4% (80.0% to 91.4%) | | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 96.4% | | | 91.0% to 99.0% | | |
| **Clinical specificity d / (b + d)** | | 61.4% | | | 45.5% to 75.6% | | |
| **PPV a / (a + b)** | | 86.3% | | | 79.0% to 91.8% | | |
| **NPV d / (c + d)** | | 87.1% | | | 70.2% to 96.4% | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 2.49\*\*\* | | | 1.72 to 3.36\*\*\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.06\*\*\* | | | 0.02 to 0.16\*\*\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 42.485\*\*\* | | | 13.211 to 136.631\*\*\* | | |
| Comments:  Reviewer’s calculations of values and 95% CIs match those reported in the paper.  \* Neoplastic polyps defined as tubular adenoma, villous adenoma, high-grade dysplasia or cancer.  \*\* Non-neoplastic defined as hyperplastic, sessile serrated adenoma/polyp or inflammatory.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results - Standard-view NBI, high confidence diagnoses of diminutive polyps located in the left colon (n = 122)** | | | | | | | |
|  | **Adenomatous\* polyps on histopathology** | | **Hyperplastic\*\* polyps on histopathology** | | | | **Total** |
| **Index test positive** | (a) 64\*\*\* | | (b) 9\*\*\* | | | | 73\*\*\* |
| **Index test negative** | (c) 3\*\*\* | | (d) 46\*\*\* | | | | 49\*\*\* |
| **Total** | 67\*\*\* | | 55\*\*\* | | | | 122 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90.2% (95% CI, 83.4% to 94.8%) | | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | 95.5% | | 87.5% to 99.1% | | | |
| **Clinical specificity d / (b + d)** | | 83.6% | | 71.2% to 92.2% | | | |
| **PPV a / (a + b)** | | 87.7% | | 77.9% to 94.2% | | | |
| **NPV d / (c + d)** | | 93.9% | | 83.1% to 98.7% | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.84\*\*\* | | 3.20 to 10.63\*\*\* | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.05\*\*\* | | 0.02 to 0.16\*\*\* | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 109.037\*\*\* | | 27.973 to 425.024\*\*\* | | | |
| Comments:  Reviewer’s calculations of values and 95% CIs match those reported in the paper.  \* Neoplastic polyps defined as tubular adenoma, villous adenoma, high-grade dysplasia or cancer.  \*\* Non-neoplastic defined as hyperplastic, sessile serrated adenoma/polyp or inflammatory.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results - Standard-view NBI, high confidence diagnoses of diminutive polyps (n = 445\*); data extracted from McGill paper73** | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | | **Total** |
| **Index test positive** | (a) Incalculable\*\* | | (b) Incalculable | | | | Incalculable |
| **Index test negative** | (c) Incalculable | | (d) Incalculable | | | | Incalculable |
| **Total** | Incalculable | | Incalculable | | | | 445 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 87.0% of polyps correctly classified. (CIs not reported.) | | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | Incalculable | | Incalculable | | | |
| **Clinical specificity d / (b + d)** | | Incalculable | | Incalculable | | | |
| **PPV a / (a + b)** | | Incalculable | | Incalculable | | | |
| **NPV d / (c + d)** | | *Overall:*  92.6%  *NPV in first half of study:* 88.0%  *NPV in second half of study:* 95.8% | | *Overall:*  CIs not reported.  *First half of study:*  75.7% to 95.5%  *Second half of study:*  88.3% to 99.1% | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | Incalculable | | Incalculable | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | Incalculable | | Incalculable | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | Incalculable | | Incalculable | | | |
| Comments:  \* Please note that Kaltenbach paper5 reported that 323 diminutive polyps in the standard-view arm were assessed with high confidence (results extracted above), while the McGill paper73 (results reported here) suggests that 445 diminutive polyps were assessed with high confidence (not explicitly stated, but reviewer’s interpretation based on the definition of NPV in the paper, which was calculated for high confidence assessments of diminutive polyps only, and polyp numbers provided on page 203). Therefore the results reported and calculated here differs to those above for this subgroup of polyps.  \*\* 2x2 table data, and hence other sensitivity, specificity etc. values, are incalculable, as insufficient data are available to accurately calculate these. For example, the reviewer has identified two different solutions for the 2x2 table that produce the reported accuracy and NPV values. These are: 1. a = 137, b = 38, c = 20 and d = 250, and 2. a = 187, b = 42, c = 16 and d = 200. | | | | | | | |
| **Interpretability of test** | | Not reported | | | | | |
| **Inter-observer agreement** | | Not reported | | | | | |
| **Intra-observer agreement** | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | | |
| **Adverse events** | | The authors report that there was no postpolypectomy bleeding, coagulation syndrome, perforation, or optical misdiagnosis of advanced histology. | | | | | |
| **High confidence optical diagnosis** | | In the standard-view arm, the endoscopists made their histology prediction of 323 of the 445 (72.6%; 95% CI, 68.2% to 76.7%) diminutive polyps with high confidence. Please see 2x2 table above. | | | | | |
| **Low confidence optical diagnosis** | | Calculated by reviewer, based on number of high confidence predictions reported (see above): 122 of 445 (27.4%) in standard-view arm. | | | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | | |
| **Recommended surveillance interval** | | Surveillance intervals were assigned using the following guidelines (the Multi-Society guidelines):  Lieberman DA, Rex DK, Winawer SJ et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57.102  Rex DK, Kahl CJ, Levin B et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastronenterology 2006; 130:1865-71.  In the standard-view colonoscopy arm, 259 of 281 patients were (92.2%) were assigned the correct surveillance interval during optical diagnosis (i.e. this is the agreement with histopathology).  When assigning surveillance intervals based on high confidence optical diagnosis of diminutive polyps combined with histopathology results for all other polyps, of the 210 patients in the standard-view arm with polyps, 200 (95.2%) received the correct recommended interval. 7 (3.3%) were given an earlier recommended interval (told to return 2.4+/-1.1 years earlier) and 3 (1.4%) were given a delayed recommended interval (delayed by 3.0+/-1.7 years).  Agreement in surveillance intervals assigned when using standard-view also reported for each of the first and second halves of the study in the McGill paper73; these data are not extracted here. | | | | | |
| **Length of time to perform the colonoscopy** | | Procedure time: 12 s (standard-view) (not stated if this is the mean or median).  Mean inspection time (arm not stated): 10 min.  Withdrawal time (standard-view) (reported in Table 1, p. 1571), not stated if mean or median (+/-SD) min, range: 10.3 (5.7), 3.3-58. | | | | | |
| **Number of outpatient appointments** | | Not reported | | | | | |
| **Health related quality of life** | | Not reported | | | | | |
| **Colorectal cancer** | | Not reported | | | | | |
| **Mortality** | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | All patients were colonoscopy for screening, surveillance or investigation of symptoms indicative of colorectal cancer. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | When multiple polyps (defined as two or more) were identified in the rectosigmoid in any one patient, a “representative sample” (Kaltenbach paper,5 p. 1570) was resected for histopathological analysis. Additionally, three polyps were not retrieved for histopathological examination (reasons not given). Otherwise, all polyps were subject to histopathological assessment (two patients did not undergo colonoscopy in the end, and missing data were imputed for these). | No |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The pathologist was blinded to the endoscopic diagnosis. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Of the 281 participants randomised to the standard-focus arm, 2 did not have a complete colonoscopy due to poor bowel preparation quality or stricture. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional, relevant publications identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The patients included in the study were undergoing colonoscopy for surveillance, screening and to investigate symptoms suggestive of colorectal cancer. More detailed information about the indications was not provided, but the patient population appears to be very relevant to the range of patients of interest in this appraisal. This study was conducted in three study centres. Five endoscopists carried out the colonoscopies and all received training in optical diagnosis before the study started.5 Three were already experienced in using NBI. The authors point out that all the endoscopists had a history of performing high volumes of colonoscopies, and that they did not compare high and low volume endoscopists.73 The findings may therefore not generalise to less experienced endoscopists. The authors imply on p. 1575 of the Kaltenbach paper5 that the three study centres were academic centres (this is not explicitly stated in the paper). The authors state that the literature shows that non-academic centres have not achieved high levels of diagnostic accuracy and that therefore the results of this study may not generalise to community practice. |

**Kang et al.78**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | | **Diagnostic tests** | | **Participants** | | | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Comparison of the diagnostic performances of NBI and FICE in differentiating neoplastic from non-neoplastic colorectal polyps (<10 mm) during real-time screening colonoscopy.  **First author:** Kang et al.  **Publication year:** 2015  **Country:** South Korea  **Study design:** RCT  **Number of centres:** 1 (Seoul National  University Hospital Healthcare System Gangnam Center)  **Funding:** Not reported  **Competing interests:** None | | **Index test:** Endoscopists predicted histology in real-time using narrow band imaging (NBI) or flexible spectral imaging colour enhancement (FICE) (adenoma or non-adenomatous polyp; also  recorded the location,  morphology and estimated size of polyp). After a polyp was detected in white light, either the NBI or FICE modes were used to predict the polyp histology.  Procedures were performed using either a colonoscope (CFH260ZI;  Olympus, Optical, Tokyo, Japan) with a processor capable of NBI and high definition imaging (EVIS 260 - Lucera Spectrum Olympus Optical) or a high-resolution zoom endoscopes (EC 590ZW; Fujinon, Inc., Saitama, Japan) with an EPX 4400 processor (Fujinon, Inc., FICE technology). The zoom function of the device was not used for this study.  **Reference standard:**  Histopathology | | **Number of participants:** 1005 (n=50 excluded after randomisation. NBI n=28 poor bowel preparations;  FICE: n=20 poor bowel preparation, n=2 failed colonoscopy)  NBI: n=475  FICE: n=480  **Sample attrition/dropout:**  *Excluded:* n=556(calculated by reviewer)  NBI: n=262 lacking polyps, n=10 polys measuring ≥10 mm;  FICE: n=272 lacking polyps; n =12 polys measuring ≥10 mm.  *Used in analysis:* n= 399 (with 851 colorectal polyps)  NBI: n=203 (463 polyps);  FICE: n=196 (388 polyps).  **Selection of participants:**  Consecutive asymptomatic individual who attended the centre for colorectal cancer screening.  **Inclusion criteria for study entry:** as below  **Exclusion criteria for study entry:** those with or with histories of inflammatory bowel disease, polyposis syndrome, colorectal disease-related symptoms or signs (e.g., recent bowel habit change, unexplained weight loss, anaemia, or lower GI tract bleeding not attributable to haemorr-hoids), family history of colorectal cancer (at least one first-degree relative with colorectal cancer diagnosed at any age), history of colorectal cancer or polyps, surgical resection of colon or rectum, intestinal tuberculo-sis, coagulopathy, and incomplete examination of the entire colon because of failure to reach the cecum or inadequate bowel preparation. | | | | | **Primary outcome of study:** sensitivity, specificity, positive and negative predictive values and overall accuracy of differentiating neoplastic from non-neoplastic polyps using NBI and FICE.  **Other relevant outcomes:** effect of polyp size and location (subgroup analysis – subgroup analyses results by polys location not reported); NBI and FICE system performances compared with the histopathology results.  Total examination time (all polyps) also reported.  **Recruitment dates:** August 2010 to  February 2011. | |
| **Participant characteristics** | | | | | | | **NBI (n=203)** | **FICE (n=196)** | | ***p* value** |
| Total sample: Age years, mean (SD) | | | | | | | 54.7 (8.9) | 54.3 (9.0) | | 0.681 |
| **Other key patient characteristics** | Total sample: Male gender, n (%) | | | | | | 139 (68.5) | 149 (76.0) | | 0.093 |
| Total sample: Polyp, n (%) | | | | | |  |  | | 0.899 |
| 1-2 | | | | | | 148 (72.9) | 144 (73.5) | |  |
|  | ≥3 | | | | | | 55 (27.1) | 52 (26.5) | |  |
|  | Polyps size 0-5 mm, n (%) | | | | | | 384 (82.9) | 321 (82.7) | |  |
|  | 0-5 mm subgroup: Histology according to polyp size, n (%) | | | | | |  |  | |  |
|  | Adenoma | | | | | | 232 (60.4) | 192 (59.8) | | 0.871 |
|  | Non-adenoma | | | | | | 152 (39.6) | 129 (40.2) | |  |
|  | Total sample: Average no. of polyps per participant, (range) | | | | | | 2.2 (1-13) | | |  |
| 82.8 % of all polyps were diminutive polyps measuring ≤5 mm | | | | | | | | | |
| **Endoscopist experience and training** | | | 4 board-certified staff endoscopists, each having performed more than 4000 colonoscopies. Endoscopists had no prior experience with NBI or FICE, but endoscopists performed a pilot study involving a minimum of 50 polyp examinations. Laminated reference sheets containing pictures and sketches were posted in each endoscopy room, showing the adenoma or non-adenomatous polyp classifications. During the study feedback was provided every 2 weeks on the accuracy of endoscopic predictions as compared to the histopathological diagnosis by the expert. | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | | *Polyp classification:*  Presumed adenomatous if: polyp was brown in colour, had increased vascular density, or round or tubulogyrus pattern were observed.  Presumed non-adenomatous if: surface showed normal or bland appearance, or if avascular or faint vascular patterns were observed. Four supporting references for these criteria are provided in the paper)  *Histological classification:* conducted by a single expert pathologist (blinded to the endoscopic images and optical predictions) classified all specimens according to the World Health Organization guidelines and the serrated lesions according to the diagnostic criteria proposed by Snover et al., 2011 (references provided in paper). | | | | | | | |
| **Sample size calculation** | | | The authors hypothesised that the diagnostic sensitivities of NBI and FICE were identical for identifying adenoma and calculated that a  minimum sample size of 343 polyps in each group provided a statistically significant result with a difference in proportions of at least 5% (approximately 85 vs. 90 %; 80 % power and significance level 0.05) - planned enrolment a minimum of 430 participants per arm after consideration of the polyp detection rate and dropout rate from their previous data. | | | | | | | |
| **Results** | | | | | | | | | | |
| **NBI ≤5 mm subgroup** | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | | (a) 190\* | | | (b) 37\* | | | 227 | |
| **Index test negative** | | | (c) 42\* | | | (d) 115\* | | | 157 | |
| **Total** | | | 232 | | | 152 | | | 384 | |
| **Accuracy** [a+d]/[a+b+c+d]) | | | 0-5 mm subgroup 79.4 % (95 % CI, 75.5% to 83.6%) | | | | | | | |
| ***Diagnosis ≤5 mm subgroup*** | | | | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | | | | 81.9% | | | 77.1% to 87.0% | |
| **Clinical specificity d / (b + d)** | | | | | | 75.7% | | | 69.2% to 82.9% | |
| **PPV a / (a + b)** | | | | | | 83.7% | | | 79.0% to 88.7% | |
| **NPV d / (c + d)** | | | | | | 73.2% | | | 66.6% to 80.5% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 3.36\* | | | 2.53 to 4.48\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.24\* | | | 0.18 to 0.32\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 14.1 | | | 8.5 to 23.2 | |
| **FICE ≤5 mm subgroup** | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | | (a) 143\* | | | (b) 15\* | | | 158 | |
| **Index test negative** | | | (c) 49\* | | | (d) 114\* | | | 163 | |
| **Total** | | | 192 | | | 129 | | | 321 | |
| **Accuracy** [a+d]/[a+b+c+d]) | | | 0-5 mm subgroup 80.1% (95 % CI, 75.8% to 84.6%) | | | | | | | |
| ***Diagnosis ≤5 mm subgroup*** | | | | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | | | | 74.5% | | | 68.6% to 80.9% | |
| **Clinical specificity d / (b + d)** | | | | | | 88.4% | | | 82.9% to 94.2% | |
| **PPV a / (a + b)** | | | | | | 90.5% | | | 85.9% to 95.3% | |
| **NPV d / (c + d)** | | | | | | 69.9% | | | 63.2% to 77.3% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 6.41\* | | | 3.95 to 10.38\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.29\* | | | 0.22 to 0.37\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 22.2 | | | 11.8 to 41.6 | |
| Comments: \* Calculated by reviewer.  Calculations agree with values reported in paper, (although approximation of rounding differs), but CIs differ. | | | | | | | | | | |
| **Interpretability of test** | | | | | Not reported | | | | | |
| **Inter-observer agreement** | | | | | Not analysed | | | | | |
| **Intra-observer agreement** | | | | | Not analysed | | | | | |
| **Test acceptability (patients / clinicians)** | | | | | Not reported | | | | | |
| **Adverse events** | | | | | Not reported | | | | | |
| **High confidence optical diagnosis** | | | | | Not reported | | | | | |
| **Low confidence optical diagnosis** | | | | | Not reported | | | | | |
| **Number of polyps designated to be left in place** | | | | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | | Not reported | | | | | |
| **Recommended surveillance interval** | | | | | Not reported | | | | | |
| **Total sample: Length of time to perform the colonoscopy –mean min (SD)** | | | | | NBI: 18.6 (8.6)  FICE 18.6 (7.4); p=0.947 | | | | | |
| **Number of outpatient appointments** | | | | | Not reported | | | | | |
| **Health related quality of life** | | | | | Not reported | | | | | |
| **Colorectal cancer** | | | | | Not reported | | | | | |
| **Mortality** | | | | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | The two groups of patients were based on average-risk adults undergoing screening colonoscopies. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? | The real time virtual chromo-endoscopy assessment and the polyp resection for histopathological analysis appear to be performed at the same time. | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The whole sample received verification using the intended reference standard. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Experienced gastrointestinal  histopathologist, blinded to endoscopic images and optical predictions, classified all specimens according to WHO guidelines. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | Not stated, but believed to be none. | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated, but believed to be none. | No |
| 11 | Were withdrawals from the study explained? | Of 1005 patients randomised, 606 were excluded from the analysis for a variety of reasons, which were provided (i.e. poor bowel preparations, failed colonoscopy, lacked polyps and polys ≥10 mm). | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant reverences were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| While the sample was based on average-risk adults undergoing screening colonoscopies, patients are from South Korea and it is unclear how representative the population is of the patient population in the UK, and how similar endoscopists training is compared to training received in the NHS. Study was performed in a single centre, so the results may not be applicable to a wider range of settings. |

**Ladabaum et al.6**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | | | | **Diagnostic tests** | | | | | | | | | | **Participants** | | | | | | | | | **Outcome measures** | | | | |
| **Condition being diagnosed / detected:**  Optical diagnosis of colorectal polyps as hyperplastic or adenoma or other (study also included an ex vivo computer training phase which has not been data extracted).  **First author:** Ladabaum et al.  **Publication year:** 2013  **Country:** USA  **Study design:** Prospective cohort  **Number of centres:**1 (single-specialty practice, Ann Arbor, Michigan, USA)  **Funding:** Grant from division of Gastroenterology at Stanford University School of Medicine.  **Competing interests:** One of the eight authors had received research support and serves on the speaker’s bureau for Olympus Corp. The remaining authors disclosed no conflicts. | | | | **Index test:**  Endoscopists predicted histology in real-time using narrow band imaging (NBI) (hyperplastic or adenoma; or other with explanation) and indicated level of confidence about their prediction (‘high’ if polyps had one or more features associated with one histology and no features associated with the other; ‘low’ if there was uncertainty regarding features or if there were features of both histologies).  NBI performed in endoscopy suites equipped with Evis Exera II CV-180 processors, CF-H180AL and PCF-H180AL colonoscopes (Olympus America, Center Valley, PA) and high definition monitors.  **Reference standard:**  Histopathology | | | | | | | | | | **Number of participants:** Participants were considered to be the endoscopists n=12  **Sample attrition/dropout:** Unclear whether any endoscopists dropped out.  Fourteen polyps with missing size were excluded.  **Selection of participants:** Endoscopists were community-based gastroenterologists. No details on how they were recruited to the study.  Colonoscopies included were any (including non-screening examinations) in which at least one polyp was removed.  **Inclusion criteria for study entry:** as above  **Exclusion criteria for study entry:** none reported. | | | | | | | | | **Primary outcome of study:** The proportion of endoscopists achieving 90% accuracy in differentiating independent diminutive (≤5 mm) adenomas from nonadenomas.  **Other relevant outcomes:** Nature of the learning curves, test performance characteristics, agreement between surveillance recommendations with versus without the use of NBI.  **Diagnostic threshold:** N/A  **Recruitment dates:** Study took place March 2011 to March 2012. | | | | |
| **Participant characteristics** note that participants were considered to be the endoscopists in this study. No details provided regarding the patients. | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Age, years, mean (SD)** | | | | Not reported | | | | | | | | | | | | | | | | | | | | | | | |
| **Other key patient characteristics (list)** | | | | Not reported | | | | | | | | | | | | | | | | | | | | | | | |
| **Endoscopist experience and training** | | | | Endoscopy practice experience in years, median (Interquartile range, [IQR]) 12 (6-21)  Colonoscopy volumea per year, median (IQR) 901 (803 - 1105)  Adenoma detection ratea, median (IQR) 35% (30% - 38%)  Prior to enrolment in this study no participants had formal training or significant experience with NBI. The first part (ex vivo phase) of the study consisted of 3 self-administered, computerized components that participants completed at their own pace during the first study week: a pretest, a learning module on the NICE classification, and a posttest. Results of the second part (in vivo phase) of the study therefore reflect the outcomes from endoscopists newly trained in NBI, the nature of their learning curves was a secondary outcome for the study (not data extracted). | | | | | | | | | | | | | | | | | | | | | | | |
| a - In the year before study entry | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | | | Posters showing the NICE classification and photo examples present in endoscopy suites. The ex vivo study phase (not data extracted) included a learning module on the NICE classification. | | | | | | | | | | | | | | | | | | | | | | | |
| **Sample size calculation** | | | | The authors calculated a priori that with 12 participants their study design provided 79% power to detect an 80% success rate, based on a one-sided exact binomial test with an 8% type I error rate. | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: sub-sample of diminutive polyps (≤5 mm)** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | **Adenomatous polyps on histopathology** | | | | | | | | | | **Hyperplastic polyps on histopathology** | | | | | | | | | **Total** | | | | |
| **Index test positive** | | | | (a) 995\* | | | | | | | | | | (b) 252\* | | | | | | | | | 1247\* | | | | |
| **Index test negative** | | | | (c) 155\* | | | | | | | | | | (d) 456\* | | | | | | | | | 611\* | | | | |
| **Total** | | | | 1150 (62%)\* | | | | | | | | | | 708 (38%)\* | | | | | | | | | 1858 | | | | |
| **Accuracy, mean (95% CI)** | | | | 78.1% (73.7 to 82.5) | | | | | | | | | | | | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | | | | | | | | | **Value** | | | | | | | | | | **95% CI** | | | | |
| **Clinical sensitivity a / (a + c)** | | | | | | | | | | | | | 86.5% | | | | | | | | | | 80.9 to 92.1 | | | | |
| **Clinical specificity d / (b + d)** | | | | | | | | | | | | | 64.7% | | | | | | | | | | 54.9 to 74.6 | | | | |
| **PPV a / (a + b)** | | | | | | | | | | | | | 79.8% | | | | | | | | | | 74.3 to 85.3 | | | | |
| **NPV d / (c + d)** | | | | | | | | | | | | | 75.9% | | | | | | | | | | 69.1 to 82.7 | | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | | | | | | | | 2.43\* | | | | | | | | | | 2.20 to 2.69\* | | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | | | | | | | | 0.21\* | | | | | | | | | | 0.18 to 0.24\* | | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | | | | | | | | 11.62 | | | | | | | | | | 9.24 to 14.60 | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper therefore the reviewer has imputed these. The imputed values provide the same sensitivity, PPV and NPV as reported in the paper but the value for specificity (64.4%) differs slightly to that reported in the paper (64.7%).  \* - value calculated by reviewer | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: sub-sample of diminutive polyps (≤5 mm) in the rectosigmoid region** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | | **Adenomatous polyps on histopathology** | | | | | | | | | | **Hyperplastic polyps on histopathology** | | | | | | | | | | **Total** | | |
| **Index test positive** | | | | | (a) 186\* | | | | | | | | | | (b) 97\* | | | | | | | | | | 283\* | | |
| **Index test negative** | | | | | (c) 48\* | | | | | | | | | | (d) 309\* | | | | | | | | | | 357\* | | |
| **Total** | | | | | 234 | | | | | | | | | | 406\* | | | | | | | | | | 640 | | |
| **Accuracy, mean (95% CI)** | | | | | 77.4 (69.1 to 85.3) | | | | | | | | | | | | | | | | | | | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper. The imputed values results in slightly different values for sensitivity (79.5% vs 79.4% reported in paper), specificity (76.1% vs 76.3% reported in paper), PPV (65.7 vs 66.3 in paper), NPV (86.6 vs 87.4 in paper) and accuracy (77.3 vs 77.4 in paper).  \* - value calculated by reviewer | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: sub-sample of diminutive polyps (≤5 mm) in region proximal to the rectosigmoid** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | | | **Adenomatous polyps on histopathology** | | | | | | | | | | | **Hyperplastic polyps on histopathology** | | | | | | | | | **Total** | |
| **Index test positive** | | | | | | (a) 806\* | | | | | | | | | | | (b) 151\* | | | | | | | | | 957\* | |
| **Index test negative** | | | | | | (c) 108\* | | | | | | | | | | | (d) 149\* | | | | | | | | | 257\* | |
| **Total** | | | | | | 914 | | | | | | | | | | | 300\* | | | | | | | | | 1214 | |
| **Accuracy, mean (95% CI)** | | | | | | 79.3 (74.7 to 83.9) | | | | | | | | | | | | | | | | | | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper. The imputed values results in slightly different values for PPV (84.2 vs 85.0 in paper), NPV (58.0 vs 57.3 in paper) and accuracy (78.7 vs 79.3 in paper).  \* - value calculated by reviewer | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: comparison of the sub-sample of diminutive polyps (≤5 mm) in the rectosigmoid region versus proximal to rectosigmoid** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ***Diagnosis*** | | | **Rectosigmoid n=640** | | | | | | | | **Proximal to rectosigmoid n=1214** | | | | | | | | | | **Mean (SD) difference** | | | **p value** | | | |
| **Adenoma (% of polyps)** | | | 234 (36.6) | | | | | | | | 914 (75.3) | | | | | | | | | |
| **Clinical sensitivity, mean (95% CI)** | | | 79.4 (67.9 to 90.9) | | | | | | | | 88.2 (82.2 to 94.2) | | | | | | | | | | -8.8 (18.0) | | | 0.121 | | | |
| **Clinical specificity, mean (95% CI)** | | | 76.3 (66.1 to 86.6) | | | | | | | | 49.7 (34.7 to 64.6) | | | | | | | | | | 26.7 (22.8) | | | 0.002 | | | |
| **PPV, mean (95% CI)** | | | 66.3 (50.7 to 82.0) | | | | | | | | 85.0 (81.5 to 88.5) | | | | | | | | | | -18.7 (24.6) | | | 0.024 | | | |
| **NPV, mean (95% CI)** | | | 87.4 (82.5 to 92.4) | | | | | | | | 57.3 (38.4 to 76.2) | | | | | | | | | | 30.1 (30.7) | | | 0.006 | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | 3.35 \* | | | | | | | | 1.75 \* | | | | | | | | | | Not reported | | | Not reported | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | 0.27 \* | | | | | | | | 0.24 \* | | | | | | | | | | Not reported | | | Not reported | | | |
| **Diagnostic odds ratio** | | | Not reported | | | | | | | | Not reported | | | | | | | | | | Not reported | | | Not reported | | | |
| **Accuracy, mean (95% CI)** | | | 77.4 (69.1 to 85.3) | | | | | | | | 79.3 (74.7 to 83.9) | | | | | | | | | | -1.9 (13.5) | | | 0.628 | | | |
| **Results: sub-sample of diminutive polyps (≤5 mm) with low confidence assessment** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | | | | **Adenomatous polyps on histopathology** | | | | | | | | | | | | **Hyperplastic polyps on histopathology** | | | | | | | **Total** | |
| **Index test positive** | | | | | | | (a) | | | | | | | | | | | | (b) | | | | | | |  | |
| **Index test negative** | | | | | | | (c) | | | | | | | | | | | | (d) | | | | | | |  | |
| **Total** | | | | | | | 210 | | | | | | | | | | | | 158\* | | | | | | | 368 | |
| **Accuracy, mean (95% CI)** | | | | | | | 70.4 (58.9 to 82.0) | | | | | | | | | | | | | | | | | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper. The reviewer attempted to impute values but it was not possible to find values that provide a close match to the data presented in the paper.  \* - value calculated by reviewer | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: sub-sample of diminutive polyps (≤5 mm) with high confidence assessment** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | | | | | **Adenomatous polyps on histopathology** | | | | | | | | | | | | **Hyperplastic polyps on histopathology** | | | | | | | **Total** |
| **Index test positive** | | | | | | | | (a) \* | | | | | | | | | | | | (b) \* | | | | | | | \* |
| **Index test negative** | | | | | | | | (c) \* | | | | | | | | | | | | (d) \* | | | | | | | \* |
| **Total** | | | | | | | | 934 | | | | | | | | | | | | 547\* | | | | | | | 1481 |
| **Accuracy, mean (95% CI)** | | | | | | | | 81.1 (75.8 to 86.3) | | | | | | | | | | | | | | | | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper. The reviewer attempted to impute values but it was not possible to find values that provide a close match to the data presented in the paper.  \* - value calculated by reviewer | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Results: comparison of the sub-sample of diminutive polyps (≤5 mm) with low confidence assessment versus the sub-sample with a high confidence assessment.** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ***Diagnosis*** | | **Low confidence assessment n=368** | | | | | | | | **High confidence assessment n=1481** | | | | | | | | **Mean (SD) difference** | | | | | **p value** | | | | |
| **Adenoma (% of polyps)** | | 210 (57.1) | | | | | | | | 934 (63.1) | | | | | | | |
| **Clinical sensitivity, mean (95% CI)** | | 80.0% (72.7 to 87.4) | | | | | | | | 88.4% (82.2 to 94.7) | | | | | | | | -8.4 (13.1) | | | | | 0.49 | | | | |
| **Clinical specificity, mean (95% CI)** | | 88.4% (82.2 to 94.7) | | | | | | | | 44.1% (26.5 to 61.6) | | | | | | | | -24.2 (13.1) | | | | | 0.17 | | | | |
| **PPV, mean (95% CI)** | | 72.1 (59.0 to 85.3) | | | | | | | | 82.8 (77.0 to 88.6) | | | | | | | | -10.7 (21.3) | | | | | 0.111 | | | | |
| **NPV, mean (95% CI)** | | 51.8% (35.3 to 68.3) | | | | | | | | 78.3% (69.6 to 87.0) | | | | | | | | -26.5 (32.0) | | | | | 0.15 | | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 6.90 \* | | | | | | | | 1.58 \* | | | | | | | | Not reported | | | | | Not reported | | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.23 \* | | | | | | | | 0.26 \* | | | | | | | | Not reported | | | | | Not reported | | | | |
| **Diagnostic odds ratio** | | Not reported | | | | | | | | Not reported | | | | | | | | Not reported | | | | | Not reported | | | | |
| **Accuracy, mean (95% CI)** | | 70.4 (58.9 to 82.0) | | | | | | | | 81.1 (75.8 to 86.3) | | | | | | | | -10.6 (20.5) | | | | | .100 | | | | |
| Comments: Numbers of polyps identified by index test and reference test to populate the 2x2 table (i.e. values for (a), (b), (c) and (d)) are not reported in the paper and therefore the reviewer has not been able to check the reported values for sensitivity, specificity etc.  \* - value calculated by reviewer  Paper also reports outcomes above for a comparison of first versus last batch to explore learning effect and by polyp location (rectosigmoid versus proximal to rectosigmoid). Outcomes for the last 20 polyps per endoscopist, all locations high confidence and for the last 20 polyps per endoscopist, recosigmoid location, high confidence are also reported. These data have not been extracted. In addition the paper contains data for small polyps (6-9mm) which have also not been data extracted. | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Interpretability of test** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Inter-observer agreement** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Intra-observer agreement** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Test acceptability (patients / clinicians)** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Adverse events** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **High confidence optical diagnosis** | | | | | | | | | | | | |  | | | | | | | | | | | | | | |
| **- diminutive polyps (≤5 mm)** | | | | | | | | | | | | | 1481/1858 (79.7%) | | | | | | | | | | | | | | |
| **- small polyps (6-9 mm)** | | | | | | | | | | | | | 485/547 (88.7%) | | | | | | | | | | | | | | |
| **Low confidence optical diagnosis** | | | | | | | | | | | | |  | | | | | | | | | | | | | | |
| **- diminutive polyps (≤5 mm)** | | | | | | | | | | | | | 368/1858 (19.8%) | | | | | | | | | | | | | | |
| **- small polyps (6-9 mm)** | | | | | | | | | | | | | 57/547 (10.4%) | | | | | | | | | | | | | | |
| **Number of polyps left in place** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Number of polyps resected and discarded** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Number of polyps resected and sent for histological examination** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Recommended surveillance interval - All study colonoscopies** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | **Recommended surveillance interval, Number (%)** | | | | | | | | | | | | | | | **Agreement** | | | | | | | | | | | |
| **Using the Multi-Society Task Force recommendations** | **10**  **year** | | | | | | | | **5-10**  **year** | | | **3**  **year** | | | | **% agreement**  **(95% CI)** | | | | | | **k value** | | | | | **p value** |
| **- diminutive polyps assessed by NBIa** | 466 (28.3) | | | | | | | | 957 (58.1) | | | 223 (13.6) | | | | 88.4 (86.8 to 89.9) | | | | | | 0.795 | | | | | <0.001 |
| **- all polyps assessed by pathology** | 507 (30.8) | | | | | | | | 931 (56.6) | | | 208 (12.6) | | | |  | | | | | |  | | | | |  |
| **Using modified recommendations (10 year for 1-2 small adenomas)** | **10**  **year** | | | | | | | |  | | | **3**  **year** | | | |  | | | | | |  | | | | |  |
| **- diminutive polyps assessed by NBI** | 1423 (86.5) | | | | | | | |  | | | 223 (13.6) | | | | 98.4 (97.6 to 98.9) | | | | | | 0.928 | | | | | <0.001 |
| **- all polyps assessed by pathology** | 1438 (87.4) | | | | | | | |  | | | 208 (12.6) | | | |  | | | | | |  | | | | |  |
| **Recommended surveillance interval - All study colonoscopies with at least one diminutive polyp characterised with high confidence** | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|  | **Recommended surveillance interval, Number (%)** | | | | | | | | | | | | | | | **Agreement** | | | | | | | | | | | |
| **Using the Multi-Society Task force recommendations** | **10**  **year** | | | | | | | | **5-10**  **year** | | | **3**  **year** | | | | **% agreement**  **(95% CI)** | | | | | | **k value** | | | | | **p value** |
| **- diminutive polyps assessed by NBIa** | 357 (33.5) | | | | | | | | 578 (54.3) | | | 130 (12.2) | | | | 79.9 (77.4 to 82.3) | | | | | | 0.654 | | | | | <0.001 |
| **- all polyps assessed by pathology** | 402 (37.8) | | | | | | | | 547 (51.4) | | | 116 (10.9) | | | |  | | | | | |  | | | | |  |
| **Using modified recommendations (10 year for 1-2 small adenomas)** | **10**  **year** | | | | | | | |  | | | **3**  **year** | | | |  | | | | | |  | | | | |  |
| **- diminutive polyps assessed by NBI** | 935 (87.8) | | | | | | | |  | | | 130 (12.2) | | | | 96.8 (95.6 to 97.8) | | | | | | 0.844 | | | | | <0.001 |
| **- all polyps assessed by pathology** | 949 (89.1) | | | | | | | |  | | | 116 (10.9) | | | |  | | | | | |  | | | | |  |
| Comments: a - NBI optical diagnosis for diminutive polyps combined with pathologic assessment of all other polyps  Overall there were 1673 study colonoscopies and 1646 contribute data to the surveillance intervals outcome for all study colonoscopies. The reason(s) for the absence of data for 27 colonoscopies is not provided. The total number of colonoscopies with at least one diminutive polyp characterised with high confidence is not reported so it is not known whether any data are missing. For colonoscopies with at least one high-confidence diminutive polyp NBI use would have led to 136 (13%) shorter and 78 (7%) longer recommended intervals than with histopathology alone using the Multi-Society Task Force recommendations; using modified recommendations NBI use would have led to 24 (2%) shorter and 10 (1%) longer recommended intervals than with histopathology alone. When the presence of diminutive sessile serrated adenomas and traditional serrated adenomas informed surveillance intervals, the agreement between strategies was only minimally affected (data presented but not extracted).  Surveillance interval recommendations reported for only the last 20 colonoscopies per endoscopist with at least one diminutive polyp characterised with high confidence have not been extracted. | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Length of time to perform the colonoscopy** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Number of outpatient appointments** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Health related quality of life** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Colorectal cancer** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |
| **Mortality** | | | | | | | | | | | | | Not reported | | | | | | | | | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Characteristics of those undergoing colonoscopy are not described. It is likely that many of the examinations were for screening but it is specifically stated that nonscreening examinations could be included. | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real-time NBI assessment and the polyp resection for histopathological analysis occurred at the same time (i.e. during the same colonoscopy) | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps were resected for histopathology although 14 polyps were excluded from the analysis due to missing information on size. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Three community-based fellowship-trained gastrointestinal pathologists interpreted all specimens as part of routine practice and were blinded to optical diagnosis. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference test results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | There is little reporting on withdrawals from the study. It is unclear whether any endoscopists dropped out. It is known that fourteen polyps with missing size were excluded. | Unclear |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes |

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| --- |
| Summary reviewer’s comments |
| These results were obtained from 12 community gastroenterologists in the USA who had only just received training in the use of NBI and they were therefore not considered to be experts. Results may therefore not be applicable to endoscopists in other settings or with higher levels of experience. |

**Lee et al.7**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | | **Outcome measures** |
| **Condition being diagnosed / detected:**  Narrow-band imaging (NBI) compared to i-scan to determine whether diminutive colonic polyps were adenomas or non-neoplastic polyps.  **First author:** Lee et al  **Publication year:** 2011  **Country:** Korea  **Study design:** Prospective cohort  **Number of centres:** 1 (academic hospital)  **Funding:** not reported  **Competing interests:** The authors disclosed no financial relationships relevant to this publication. | **Index test:**  Endoscopists used high definition (HD) white-light colonoscopy and then NBI or i-scan without magnification to predict the histology of diminutive polyps in real-time. (Purpose of the study was to compare NBI and i-scan.)  Confidence in the endoscopic prediction was recorded as high or low.  Narrow band imaging.  HD colonoscope CF-H260AL, EVIS Lucera spectrum system, OEV-191H HDTV monitor, Olympus.  i-scan. HD colonoscope EC-3890, EPK-*i* system, Pentax. Radiforce RS110 HDTV monitor, EIZO, Ishikawa, Japan. Used in the TE-c mode (Tone Enhancement for colonic lesions).  **Reference standard:**  Histopathology. | | **Number of participants:** 142  **Sample attrition/dropout:** None  **Selection of participants:**  Consecutive patients undergoing screening or surveillance colonoscopy.  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  < 18 years-old; pregnancy; currently using antiplatelet agents or anticoagulants; history of inflammatory bowel disease, hereditary colorectal cancer or polyposis syndrome; unable to provide informed consent. | | | **Primary outcome of study:**  Not stated  **Other relevant outcomes:**  Accuracy of optical diagnosis  in differentiating adenomas from non-neoplastic polyps; Number of polyps assessed with high and low confidence; Accuracy of diagnostic assessments made with high and low confidence; Complications; Inter- and intra-observer agreement (calculated using percentage agreement and values of k statistics: slight ≤0.2; fair 0.21 – 0.4; moderate 0.41-0.6; substantial 0.61-0.80 and almost perfect 0.81-1.00).  **Diagnostic threshold:**  N/A  **Recruitment dates:**  May to October 2010 |
| **Participant characteristics** (based on 142 patients; n = 70 NBI and n = 72 i-scan) | | | | | | |
| **Age, years, mean (SD)** | NBI group: 57.98 (10.6); i-scan group: 55.4 (11.3) | | | | | |
| **Other key patient characteristics (list)** | *NBI:* male n=52 (74.3%); female n=18 (25.7%) [n and % calculated by reviewer]. *i-scan group:* male n=62 (86.1%); female n=10 (13.9%) [n and % calculated by reviewer].  Total number of diminutive polyps evaluated by NBI n = 156 (from 70 patients).  Total number of diminutive polyps evaluated by i-scan n = 140 (from 72 patients).  Note: study solely focused on diminutive polyps. | | | | | |
| **Endoscopist experience and training** | One endoscopist described as ‘experienced’ carried out the colonoscopies. However no details of the endoscopist’s experience or training are reported. | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | One of the authors (the endoscopist carrying out the colonoscopies for the study), developed a classification system for use in this study. They developed it based on pilot work involving examination of the features of colon polyps based on images produced by NBI and i-scan, cross-referenced with histological findings. | | | | | |
| **Sample size calculation** | 76 diminutive polyps per group were needed for a power of 80% to demonstrate superiority of virtual chromoendoscopy in comparison to high-definition white light, assuming a diagnostic accuracy of 60% for HD white-light and 90% for both NBI and i-scan. | | | | | |
| **Results: NBI** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 71\* | | (b) 10\* | | | 81 |
| **Index test negative** | (c) 9\* | | (d) 66\* | | | 75 |
| **Total** | 80 (51.3%) | | 76 (48.7%) | | | 156 |
| **Accuracy** | 87.8% (95% CIs: 82.6% to 92.9%) | | | | | |
| ***Diagnosis: NBI*** | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 88.8% | | | 81.8% to 95.7% | |
| **Clinical specificity d / (b + d)** | | 86.8% | | | 79.2% to 94.4% | |
| **PPV a / (a + b)** | | 87.7% | | | 80.5% to 94.8% | |
| **NPV d / (c + d)** | | 88.0% | | | 80.6% to 95.4% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 6.75\* | | | 3.77 to 12.08\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.13\* | | | 0.07 to 0.24 | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 52.07\* | | | 19.92 to 136.10\* | |
| * Reviewer has checked values reported for sensitivity, specificity, PPV and NPV using the reported index test positive and negative results. The values agree but different (slightly lower) 95% CIs were obtained.   \* calculated by the reviewer, result not reported in paper. | | | | | | |
| **Results: NBI – high confidence predictions** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 56 | | (b) 6\* | | | 62 |
| **Index test negative** | (c) 5\* | | (d) 58 | | | 63 |
| **Total** | 61\* | | 64\* | | | 125\* |
| **Accuracy**  ([a+d]/[a+b+c+d]) | High confidence overall 91.2% (114/125)\*  For predicting adenomas: 90.3% (56/62); for predicting hyperplastic polyps: 92.1% (58/63). | | | | | |
| ***Diagnosis: NBI – high confidence predictions*** | | **Value** | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 91.80%\* | | 81.90% to 97.28%\* | | |
| **Clinical specificity d / (b + d)** | | 90.62%\* | | 80.70% to 96.48%\* | | |
| **PPV a / (a + b)** | | 90.32%\* | | 80.12% to 96.37%\* | | |
| **NPV d / (c + d)** | | 92.06%\* | | 82.44% to 97.37%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 9.79\* | | 4.55 to 21.05\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.09\* | | 0.04 to 0.21\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 108.27\* | | 31.26 to 375.00\* | | |
| \* calculated by the reviewer. | | | | | | |
| **Results: NBI – low confidence predictions** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 15 | | (b) 4\* | | | 19 |
| **Index test negative** | (c) 4\* | | (d) 8 | | | 12 |
| **Total** | 19\* | | 12\* | | | 31\* |
| **Accuracy**  ([a+d]/[a+b+c+d]) | Low confidence overall 74.2% (23/31)\*  For predicting adenomas: 79.0% (15/19); for predicting hyperplastic polyps: 66.7% (8/12). | | | | | |
| ***Diagnosis: NBI – low confidence predictions*** | | **Value** | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 78.95%\* | | 54.43% to 93.95%\* | | |
| **Clinical specificity d / (b + d)** | | 66.67%\* | | 34.89% to 90.08%\* | | |
| **PPV a / (a + b)** | | 78.95%\* | | 54.43% to 93.95%\* | | |
| **NPV d / (c + d)** | | 66.67%\* | | 34.89% to 90.08%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 2.37\* | | 1.03 to 5.45\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.32\* | | 0.12 to 0.82\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 7.50\* | | 1.47 to 38.28\* | | |
| \* calculated by the reviewer.  Paper reports there were no statistically significant differences in accuracy between high- and low-confidence predictions of adenomas with NBI (p = n.s.). In contrast there were statistically significant differences in accuracy between high- and low-confidence predictions of hyperplastic polyps (p = .013). | | | | | | |
| **Interpretability of test** | | Not reported | | | | |
| **Inter-observer agreement** | | % agreement = 86.5, k value (95% CI) = 0.730 (0.623 to 0.837), representing ‘substantial’ agreement. | | | | |
| **Intra-observer agreement** | | % agreement = 89.7, k value (95% CI) = 0.795 (0.699 to 0.890), representing ‘substantial’ agreement. | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | |
| **Adverse events** | | It is stated that participants did not experience any procedure-related complications. | | | | |
| **High confidence optical diagnosis** | | High confidence predictions, n/N (%) polyps = 125/156 (80.1%)  See 2x2 table above for results. | | | | |
| **Low confidence optical diagnosis** | | Low confidence predictions, n/N (%) = 31/156 (19.9%)  See 2x2 table above for results. | | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | |
| **Recommended surveillance interval** | | Not reported | | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | | |
| **Number of outpatient appointments** | | Not reported | | | | |
| **Health related quality of life** | | Not reported | | | | |
| **Colorectal cancer** | | Not reported | | | | |
| **Mortality** | | Not reported | | | | |
|  | | | | | | |
| **Results: i-scan** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 70\* | | (b) 9\* | | | 79 |
| **Index test negative** | (c) 4\* | | (d) 57\* | | | 61 |
| **Total** | 74 (52.9%) | | 66 (47.1%) | | | 140 |
| **Accuracy** | 90.7% (85.9% to 95.5%) | | | | | |
| ***Diagnosis: i-scan*** | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 94.6% | | | | 89.4% to 99.7% |
| **Clinical specificity d / (b + d)** | | 86.4% | | | | 78.1% to 94.6% |
| **PPV a / (a + b)** | | 88.6% | | | | 81.6% to 95.6% |
| **NPV d / (c + d)** | | 93.4% | | | | 87.2 to 99.7% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 6.94\* | | | | 3.77 to 12.76\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.06\* | | | | 0.02 to 0.16\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 110.83\* | | | | 32.44 to 378.66\* |
| * Reviewer has checked values reported for sensitivity, specificity, PPV and NPV, using the reported index test positive and negative results. The values agree but slightly different 95% CIs were obtained.   \* calculated by the reviewer, result not reported in paper. | | | | | | |
| **Results: i-scan – high confidence predictions** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 50 | | (b) 5\* | | | 55 |
| **Index test negative** | (c) 3\* | | (d) 54 | | | 57 |
| **Total** | 53\* | | 59\* | | | 112\* |
| **Accuracy**  ([a+d]/[a+b+c+d]) | High confidence overall 92.9% (104/112)  For predicting adenomas: 90.9% (50/55); for predicting hyperplastic polyps: 94.7% (54/57) | | | | | |
| ***Diagnosis: i-scan – high confidence predictions*** | | **Value** | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 94.34%\* | | 84.34% to 98.82%\* | | |
| **Clinical specificity d / (b + d)** | | 91.53%\* | | 81.32% to 97.19%\* | | |
| **PPV a / (a + b)** | | 90.91%\* | | 80.05% to 96.98%\* | | |
| **NPV d / (c + d)** | | 94.74%\* | | 85.38% to 98.90%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 11.13\* | | 4.80 to 25.82\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.06\* | | 0.02 to 0.19\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 180.00\* | | 40.89 to 792.43\* | | |
| \* calculated by the reviewer. | | | | | | |
| **Results: i-scan – low confidence predictions** | | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 20 | | (b) 4\* | | | 24 |
| **Index test negative** | (c) 1\* | | (d) 3 | | | 4 |
| **Total** | 21\* | | 7\* | | | 28\* |
| **Accuracy**  ([a+d]/[a+b+c+d]) | Low confidence overall 82.1% (23/28)  For predicting adenomas: 83.3% (20/24); for predicting hyperplastic polyps: 75.0% (3/4) | | | | | |
| ***Diagnosis: i-scan – low confidence predictions*** | | **Value** | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 95.24%\* | | 76.18% to 99.88%\* | | |
| **Clinical specificity d / (b + d)** | | 42.86 %\* | | 9.90% to 81.59%\* | | |
| **PPV a / (a + b)** | | 83.33%\* | | 62.62% to 95.26%\* | | |
| **NPV d / (c + d)** | | 75.00%\* | | 19.41% to 99.37%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 1.67\* | | 0.87 to 3.19\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.11\* | | 0.01 to 0.90\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 15.00\* | | 1.23 to 183.63\* | | |
| \* calculated by the reviewer.  Paper also reports there were no statistically significant differences between the accuracy of high- and low-confidence predictions of adenomas or of hyperplastic polyps with i-scan (both p > .05). | | | | | | |
| **Interpretability of test** | | Not reported | | | | |
| **Inter-observer agreement** | | % agreement = 87.9, k value (95% CI) = 0.751 (0.640 to 0.861), representing ‘substantial’ agreement. Reviewer note: these values are reported to be for NBI in the paper, but this appears to be a typo and that these values are for i-scan. | | | | |
| **Intra-observer agreement** | | % agreement = 86.4, k value (95% CI) = 0.729 (0.616 to 0.841), representing substantial agreement. Reviewer note: these values are reported to be for NBI in the paper, but this appears to be a typo and that these values are for i-scan. | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | |
| **Adverse events** | | It is stated that participants did not experience any procedure-related complications. | | | | |
| **High confidence optical diagnosis** | | High confidence predictions, n/N (%) polyps = 112/140 (80.0%)  See 2x2 table above for results. | | | | |
| **Low confidence optical diagnosis** | | Low confidence predictions, n/N (%) polyps = 28/140 (20.0%)  See 2x2 table above for results. | | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | |
| **Recommended surveillance interval** | | Not reported | | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | | |
| **Number of outpatient appointments** | | Not reported | | | | |
| **Health related quality of life** | | Not reported | | | | |
| **Colorectal cancer** | | Not reported | | | | |
| **Mortality** | | Not reported | | | | |
| Paper reports that no significant difference (p > 0.05) was evident when NBI was compared with i-scan for the prediction of adenomas (based on reported sensitivity, specificity and accuracy of the two technologies). | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | The study included patients undergoing screening or surveillance colonoscopy and excluded those with a history of inflammatory bowel disease, hereditary colorectal cancer or polyposis syndrome. These patients are relevant to the scope of this appraisal. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Reference standard was histopathology, the gold standard. | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps removed were sent for histological examination. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All polyps removed were sent for histological examination. | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | Virtual chromoendoscopy and histopathology were performed separately. | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | An experienced gastrointestinal pathologist who was blinded to clinical information carried out the histopathological examination of the polyps. It is presumed the “clinical information” means the results of the NBI and i-scan assessments. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histopathological assessment was subsequent to the index test with NBI and i-scan. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | All polyps evaluated were diagnosed. | No |
| 11 | Were withdrawals from the study explained? | States that 142 consecutively recruited patients were included in the study. Results are reported for all 142 patients. Therefore, all selected participants appear to have been included in the analysis. No indication that any polyps were omitted from the analysis. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional references identified. |

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| Summary reviewer’s comments |
| These results were obtained from a single endoscopist described as ‘experienced’. However, the level of experience was not described further or quantified. No details of training received for NBI and i-scan were provided. The study took place at an academic hospital in Korea. The results may therefore not be applicable to endoscopists with a differing level of experience and/or training working in other settings and/or countries. |

**Longcroft-Wheaton et al. 201184**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:** In-vivo diagnosis of colorectal polyps less than 10mm.  **First author:** Longcroft-Wheaton et al  **Publication year:** 2011  **Country:** UK  **Study design:** Prospective series  **Number of centres:** 1  **Funding:** Not stated  **Competing interests:** Stated none | **Index test:** EC-530  and EC-590 Fujinon colonoscopes and EPX 4400 processor (Fujinon Corporation, Saitama City, Saitama,  Japan) without optical magnification. A flat-screen Sony 24-inch WUXGA LCD display was used (LMD-2450  MD) with a 1125 x 1080 resolution. FICE settings were preset at 4 (red channel: 520nm; green channel: 500 nm;  blue channel: 405 nm).  [reviewer note: it is unclear whether the colonoscopies are HD, but the processor is ‘HD compatible’ and the resolution of the monitor appears to be HD]  Polyps were assessed using white light endoscopy, followed by FICE, and then followed by virtual chromoendoscopy with indigo carmine dye. A diagnostic prediction was made with each technology. Only the diagnostic prediction for FICE is presented here.  **Reference standard:** Histopathology | | **Number of participants:** 89  **Sample attrition/dropout:** 124 patients underwent colonoscopy in the UK Bowel Cancer Screening Programme (BCSP), of which 89 had polyps less than 10mm [reviewer note: it is assumed that these patients were a local population of patients from the national BCSP]  **Selection of participants:** Consecutive asymptomatic patients within the UK BCSP  **Inclusion criteria for study entry:** Positive fecal occult blood test  **Exclusion criteria for study entry:** Diagnosis of a familial polyp syndrome, a diagnosis of  inflammatory bowel disease, poor bowel preparation, or  melanosis coli. | **Primary outcome of study:** Diagnosticaccuracy (sensitivity; specificity; PPV; NPV)  **Other relevant outcomes:** Surveillance intervals; costs  **Recruitment dates:** September 2009 to 2010 |
| **Participant characteristics** | | | | |
| **Age, years, mean (SD)** | Mean age = 65 years (6.7) | | | |
| **Other key patient characteristics** | Male n=70 (79%); Female n=19 (21%)  Mean polyp size = 4.7mm (range 2-9mm; SD 2.7)  Polyps less than 5mm in size (diminutive) n=155/232 (67%)  Right sided polyps n=79; Left sided polyps n=153 | | | |
| **Endoscopist experience and training** | All assessments conducted by a single endoscopist (one of the threeco-authors) with expertise in in-vivo diagnosis of polyps for over  8 years. It is not stated how much expertise or training the endoscopist had specifically with FICE. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Stated to be a previously developed and validated classification system developed by Teixeira et al. 99 Polyps were suspected to be non-neoplastic if they had a type I or type II pattern. Polyps were suspected to be adenomatous if they had a type III or IV pattern and polyps were suspected of being cancers if a type V pattern  was seen.  Serrated adenomas were treated as neoplastic for the purpose of calculating accuracy of in-vivo histology prediction (i.e., the in-vivo diagnosis was considered to be incorrect if the endoscopist called  a serrated adenoma hyperplastic).  The size, location, and morphology of polyps were defined by the Paris Classification system. | | | |
| **Sample size calculation** | The study was prospectively powered. The assumptions were made that 40% of polyps found are hyperplastic, that the true sensitivity for neoplasia with both FICE and indigo carmine would lie between 85% and 95%, and that the true specificity with FICE and indigo carmine lies between 75 and 90%. With 80% power (assuming a 5% significance level and ɸ coefficient of 0.2), 150 polyps would need to be assessed to achieve statistical significance. To demonstrate a 10% difference in the accuracy between FICE and indigo carmine, 200 polyps would need to be assessed to produce significant results. Note that the sub-group analysis of diminutive polyps may not be adequately statistically powered, though this relates to comparisons between white light, FICE and indigo carmine, which are not of direct relevance to this report. | | | |
| **Results** Sub-set of diminutive polyps n= 155 | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | **Total** |
| **Index test positive** | 75 | | 11\* | 86 |
| **Index test negative** | 15\* | | 54 | 69 |
| **Total** | 90 | | 65 | 155 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 129/155 (83%) (95% CI 77%-88%) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 83% | | 78%-88% |
| **Clinical specificity d / (b + d)** | | 83% | | 75%-89% |
| **PPV a / (a + b)** | | 87% | | 81%-91% |
| **NPV d / (c + d)** | | 78% | | 70%-84% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.92\* | | 2.85 - 8.51\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.20\* | | 0.12 - 0.32\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 24.5\* | | 10.5 - 57.6\* |
| Comments:  *\** calculated by the reviewer as not reported in the publication.  Histopathology costs associated with three different protocols for histological assessment (traditional; proposed; futuristic) are reported, together with the savings that could be achieved from the latter two. These have not been extracted here. | | | | |
|  | | | | |
|  | | | | |
| **Interpretability of test** | | Not reported | | |
| **Inter-observer agreement** | | Not reported | | |
| **Intra-observer agreement** | | Not reported | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | |
| **Adverse events** | | Not reported | | |
| **High confidence optical diagnosis** | | Not reported | | |
| **Low confidence optical diagnosis** | | Not reported | | |
| **Number of polyps designated to be left in place** | | Not reported | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | |
| **Recommended surveillance interval** | | FICE correctly predicted rescope intervals for 67 of 69 (97% CI: 89–100%) of patients using BSG and ASGE guidelines. [NB. 20 of the 89 patients were excluded from this analysis as they had additional larger polyps which would have influenced the rescope interval] | | |
| **Length of time to perform the colonoscopy** | | Not stated | | |
| **Number of outpatient appointments** | | Not stated | | |
| **Health related quality of life** | | Not stated | | |
| **Colorectal cancer** | | Not stated | | |
| **Mortality** | | Not stated | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients in the UK BCSP with a positive fecal occult blood test. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Consultant histopathologist was blinded to the diagnosis made by the endoscopist. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated, but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Not stated whether there were any withdrawals | No |

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional studies identified |

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| --- |
| Summary reviewer’s comments |
| Results are based on the use FICE after white light imaging by a single endoscopist with expertise with in-vivo diagnosis of polyps in a single centre and in an English population of patients in the BCSP with a positive faecal occult blood test (FOBT). It is not stated whether predictions were made with high or low confidence, but it is assumed that it was high confidence given that the endoscopist was experienced with in vivo diagnosis of polyps. The authors note that FICE is adequate for a resect and discard policy (i.e. due to ≥90% agreement in assignment of surveillance intervals), it is inadequate to guide the decision to leave suspected rectosigmoid polyps <5mm in place without resection, as the NPV fell below the 90% threshold in the PIVI criteria. The NPV only reached 90% when indigo-carmine dye spray was used following FICE and white light endoscopy. |

**Longcroft-Wheaton et al. 201283**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | **Outcome measures** |
| **Condition being diagnosed / detected:**  In vivo predicted diagnosis (non-neoplastic or adenomatous) of colorectal polyps <10mm in size.  **First author:** Longcroft-Wheaton  **Publication year:** 2012  **Country:** UK  **Study design:** Prospective double-blind study  **Number of centres:** One  **Funding:** Not reported  **Competing interests:** States ‘None’. | **Index test:**  Diagnosis (neoplastic or hyperplastic) was made after both white light imaging and re-assessment using FICE. The maximum time allocated for examination with each modality was 30 seconds.  FICE assessments used setting 4 (R:520nm; G:500nm; B:405nm).  Used Fujinon high definition colonoscopes containing the Fujinon super CCD at 650000 pixels (EC-530 and EC-590 colonoscopes) and an EPX-4400 processor. A flat-screen Sony 24-inch WUXGA LCD display with a 1125x1080 resolution was connected to the processor via a digital video interface connector.  This was a randomised trial but the other arm, which used standard definition colonoscopes does not meet the inclusion criteria for this review and data have not been extracted.  **Reference standard:**  Histopathology | | **Number of participants:** 143 polyps (103 of which were ≤ 5mm) from 50 participants  **Sample attrition/dropout:**  None reported  **Selection of participants:**  Positive fecal occult blood test and referred for bowel cancer screening colonoscopy on a standard screening list.  **Inclusion criteria for study entry:** as above  **Exclusion criteria for study entry:** Diagnosis of inflammatory bowel disease, familial polyp syndromes, poor bowel preparation. | | **Primary outcome of study:**  To compare the accuracy of standard and high-definition colonscopes in the diagnosis of neolastic polyps of <10mm in size (Note that only the high definition results for polyps ≤5mm in size meet the inclusion criteria for this review, other data have not been extracted).  **Secondary outcomes:**  Comparison of the accuracy of standard- and high-definition colonoscopes for the in vivo diagnosis of colonic polyps with white light imaging. Comparison of the accuracy of standard- and high-definition colonoscopes for the in vivo diagnosis of colonic polyps with FICE when used after examination with white light imaging.  **Recruitment dates:** Not reported |
| **Participant characteristics: For the high-definition group only n=85, n=50 had polyps.** | | | | | |
| **Age, years, mean (SD)** | 64 (4.2) It is not clear if this is mean age for all 85 participants or only the 50 who had polyps.  Mean polyp size 4.55 mm (range 2-10mm) | | | | |
| **Other key patient characteristics (list)** | 39/85 male (the proportion of males in the 50 participants with polyps is not reported.) | | | | |
| **Endoscopist experience and training** | A single endoscopist who was trained and experienced in in vivo diagnostic methods assessed all the polyps. No further details. | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Classification of polyps with FICE was based on vascular patterns and used the system developed by Teixeira et al.99 which is a validated system. Polyps with a type I or type II pattern were designated non-neoplastic. Polyps with a type III or IV pattern were designated adenomatous and if a type V pattern was observed a cancer was designated.  Histopathology reporting was done by an accredited colon cancer screening pathologist. In the analysis serrated adenomas were defined as neoplastic lesions. | | | | |
| **Sample size calculation** | A sample size calculation was reported for the primary outcome (comparison of high-definition and standard definition endoscopes in diagnosing neoplasia) and it was calculated that 218 polyps would be required. | | | | |
| **Results: For the subgroup of polyps <5mm** | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | a=52 | | b = 8 \* | | a+b = 60 \* |
| **Index test negative** | c = 7 \* | | d = 36 | | c+d = 43 \* |
| **Total** | a+c =59 | | b+d =44 | | a+b+c+d =103 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 85% (95% CI 76 to 91) (n/N = 88/103) | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 88% | | 80% to 94% | |
| **Clinical specificity d / (b + d)** | | 82% | | 71% to 89% | |
| **PPV a / (a + b)** | | 86.67% \* | | 75.41% to 94.06% \* | |
| **NPV d / (c + d)** | | 83.72 % \* | | 69.30% to 93.19% \* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.85 \* | | 2.57 to 9.14 \* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.15 \* | | 0.07 to 0.29 \* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 33.43 \* | | 11.13 to 100.40 \* | |
| \* = calculated by reviewer  Comments: Reviewer obtained different 95% CIs for sensitivity and specificity that those reported in the paper (77.07% to 95.09% and 67.29% to 91.81% respectively). | | | | | |
| **Interpretability of test** | | Not reported | | | |
| **Inter-observer agreement** | | Not reported | | | |
| **Intra-observer agreement** | | Not applicable | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | |
| **Adverse events** | | Not reported | | | |
| **High confidence optical diagnosis** | | Not reported | | | |
| **Low confidence optical diagnosis** | | Not reported | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | |
| **Recommended surveillance interval** | | Predicted surveillance intervals used the British Society of Gastroenterology (BSG) and ASGE guidelines and were performed on a per patient basis. Patients in whom larger lesions were found that would require histological examination were excluded.  12 patients in the high-definition group had additional lesions >10mm which would have required histology to set the surveillance interval so these were excluded from this analysis.  Correct surveillance interval using BSG guidelines = 100% (38/38)  Correct surveillance interval using ASGE guidelines = 100% (38/38).  Note that this analysis was not limited to patients with polyps ≤5mm. | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | |
| **Number of outpatient appointments** | | Not reported | | | |
| **Health related quality of life** | | Not reported | | | |
| **Colorectal cancer** | | Not reported | | | |
| **Mortality** | | Not reported | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | UK based study of patients with a positive fecal occult blood test and referred for bowel cancer screening colonoscopy. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Double blind study. The consultant histopathologist was blinded to the diagnosis made by the endoscopist. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histopathology takes place after FICE assessment | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | No results reported as being uninterpretable or intermediate. | NO |
| 11 | Were withdrawals from the study explained? | All data used for 2x2 table but 12 participants excluded from analysis of surveillance intervals due to presence of lesion >10mm. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional papers identified. |

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| --- |
| Summary reviewer’s comments |
| The participants in this UK study are likely to be representative of participants in the UK generally (although only n=50). Only a single endoscopist at a single centre was involved so it is not clear how representative the results are to UK endoscopists and centres generally. |

**Paggi et al. 20158**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:**  Discriminating neoplastic from non-neoplastic polyps by NBI  **First author:** Paggi  **Publication year**: 2015  **Country:** Italy  **Study design:** Prospective observational study  **Number of centres:** One (a community hospital)  **Funding:** Not stated  **Competing interests:** None | **Index test:**  Endoscopists used NBI to evaluate all diminutive polyps identified under white light. High confidence categorisations of adenoma or non-adenoma were recorded.  Used standard high definition colonoscopes (HDTV Olympus 180 Exera; Olympus, Tokyo, Japan) or dual-focus colonoscopes (HDTV Olympus 190 Exera) [only one room of four was equipped with the 190 technology and use of the colonoscopes depended on scheduling issues. Results using the near focus mode of the 190 colonoscopes do not meet the criteria for this review and have not been extracted.]  **Reference standard:**  Resection of all polyps into separate jars for pathological examination. | | **Number of participants:**  284 participants with at least one diminutive polyp. A total of 465 diminutive polyps were identified from an overall total of 656 polyps. Of these 446 were characterised with high confidence, 220 of these using the 180-HD colonoscope which meets the inclusion criteria for this review.  **Sample attrition/dropout:**  None apparent.  **Selection of participants:**  Only patients with at least one diminutive polyp were included in the analysis  **Inclusion criteria for study entry:**  Consecutive adult outpatients referred for colonoscopy categorised as screening, surveillance or symptoms with at least one diminutive polyp (<5mm).  **Exclusion criteria for study entry:** medical history of colorectal cancer, inflammatory bowel disease, hereditary polyposis syndromes, hereditary nonpolyposis colorectal cancer; inadequate bowel preparation (used the Aronchick scale: more than 10% mucosa not visualised); cecal intubation not achieved or indicated; polyps not resectable due to ongoing anticoagulation, or polyps not retrieved for pathological assessment. | **Primary outcome of study:**  The agreement between endoscopy- and histology-directed surveillance strategies, by applying NBI-driven resect and discard strategy, according to the PIVI statement44 (after the implementation of a retraining and monitoring initiative)  **Secondary outcomes:**  Diagnostic performance (sensitivity, specificity, PPV, NBV, positive and negative likelihood ratios) of NBI for adenoma diagnosis of diminutive polyps; diagnostic performance of NBI in the rectosigmoid; evaluation of the impact of adopting ESGE guidelines on the adequacy of endoscopy-based postpolypectomy surveillance predictions.107  Predefined subgroup analyses: operative characteristics of NBI for diminutive polyps according to the 180HD or 190HD technology; NBI diagnostic performances and agreement between endoscopy and histology based postpolypectomy surveillance predictions for individual endoscopists.  **Recruitment dates:** Between October 2013 and February 2014 |
| **Participant characteristics** (for the 284 participants with at least one diminutive polyp. Number of participants assessed using the 180-HD colonoscope not reported). | | | | |
| **Age, years, mean (SD)** | 61.3 (18.2) | | | |
| **Other key patient characteristics (list)** | Males, n (%) = 179 (63.0)  Colorectal cancer family history, n (%) = 41 (14.4)  Indication for colonoscopy, n (%): screening =121 (42.6); surveillance = 79 (27.8); symptoms = 84 (29.6) | | | |
| **Endoscopist experience and training** | Four endoscopists described as ‘highly experienced’ who had ‘used NBI technology regularly since 2009 (more than 200 exams per year per endoscopist)’. The four endoscopists had participated in an earlier study on NBI characterisation and had achieved different levels of performance (these are not reported).  Before the study all the endoscopists undertook a 1-hour training session with pre- and post-test assessments of a set of endoscopic images to standardise the classification of adenomatous and hyperplastic lesions. Every 2 months there were “refresh” sessions regardless of performance level. The “refresh” sessions included pre-test and post-test performance evaluation and reference sets of 20 different endoscopic images or videos of NBI classified diminutive polyps (either adenomatous or hyperplastic). A collective discussion was held at the end of the session to evaluate cases where a disagreement between histology and NBI evaluation had occurred. All image sets were available to the endoscopists to consult at any time.  Each endoscopist received private monthly feedback on sensitivity and specificity of NBI for adenoma diagnosis in diminutive polys as part of the internal quality assurance program which also included other routinely monitored quality measured e.g. cecal intubation and adenoma detection rates. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | High confidence categorisations of adenoma or non-adenoma were made based on published criteria1 and shown below:   |  |  |  | | --- | --- | --- | | **NBI Features** | **Predictive of adenomatous polyp** | **Predictive of hyperplastic polyp** | | Colour | Browner than the background | Same or lighter than surrounding mucosa | | Vascular pattern | Brown vessels surrounding white structures | None or isolated lacy vessels coursing across the lesion | | Surface pattern | Oval, tubular, or branched white structures surrounded by brown | Homogeneous absence of surface pattern, or dark or white spots of uniform size. |   Diminutive polyps where only a low confidence prediction could be made or in cases where the morphological features led to a suspicion of malignancy (e.g. depressed or ulcerated lesions) were not evaluated with NBI but were sent to pathology. | | | |
| **Sample size calculation** | It was calculated that 280 patients with at least 1 diminutive polyp would be required based on an assumption of a 90% agreement between the endoscopy- and histology-directed strategies for surveillance and 3% precision of the estimates. Assuming an estimated prevalence of having at least one polyp of 63% resulted in the need to enrol 444 patients. | | | |
| **Results** *[subgroup of 220 diminutive polyps assessed without magnification (i.e. 180-HD colonoscope, all high confidence assessments)]* | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | **Total** |
| **Index test positive** | a = 140 | | b = 15 | a+b = 155 |
| **Index test negative** | c = 11 | | d = 54 | c+d = 65 |
| **Total** | a+c = 151 | | b+d =69 | a+b+c+d = 220 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 88.2% (95% CI 83.9% to 92.5%) | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 92.7% | | 89.3% to 96.2% |
| **Clinical specificity d / (b + d)** | | 78.2% | | 72.7% to 83.7% |
| **PPV a / (a + b)** | | 90.32% \* | | 84.54% to 94.48% \* |
| **NPV d / (c + d)** | | 83.08 % \* | | 71.73% to 91.24% \* |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.26 \* | | 2.72 to 6.69 \* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.09 \* | | 0.05 to 0.17 \* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 45.8 \* | | 19.8 to 106.02 \* |
| Comments: Using the reported values for the 2x2 table the reviewer obtained the same point estimates as reported but slightly different confidence intervals. Results from the subgroup of polyps in the rectosigmoid have not been extracted because they are not presented separately for the 180-HD instrument.  *\** values calculated by the reviewer. | | | | |
| **Interpretability of test** | | Not reported | | |
| **Inter-observer agreement** | | Not reported | | |
| **Intra-observer agreement** | | Not reported | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | |
| **Adverse events** | | Not reported | | |
| **High confidence optical diagnosis** | | Only high confidence NBI characterisations were recorded hence all the 180 colonoscope diagnoses were made from high confidence characterisations.. | | |
| **Low confidence optical diagnosis** | | Not reported separately for the 180 colonoscope.  However it is known that 19/465 (4.1%) diminutive polyps were categorized after evaluation by NBI with low confidence and were therefore sent directly for pathological evaluation (but this information was not broken down by the colonoscope used and may therefore include polyps assessed using the near-focus option of the 190-HD colonscope). | | |
| **Number of polyps designated to be left in place** | | Not reported | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | |
| **Recommended surveillance interval** | | High confidence NBI histology predictions for diminutive polyps were merged with histopathological assessment of other polyps to generate an endoscopy-based surveillance interval. This was compared with the surveillance interval that would be recommended using pathological findings. Two guidelines (the European107 and the US Multi-Society Task Force American Cancer Society guideline102) were used to guide recommended follow- up intervals for each patient (i.e. a patient level analysis).  Results are reported only for the overall group, not separately for those patients examined with the 180-HD colonoscope (i.e. without near focus) and thus have not been extracted here. | | |
| **Length of time to perform the colonoscopy** | | Not reported | | |
| **Number of outpatient appointments** | | Not reported | | |
| **Health related quality of life** | | Not reported | | |
| **Colorectal cancer** | | Not reported | | |
| **Mortality** | | Not reported | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients receiving colonoscopy for screening, surveillance or symptoms | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? |  | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Paper does not state whether the histopathologist(s) were blind to the NBI characterisation. | Unclear |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | No withdrawals or missing data apparent. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes |

|  |
| --- |
| Summary reviewer’s comments |
| This study included endoscopists who were described as ‘highly experienced’ and who also undertook training and regular review as part of the study. The results may therefore not be generalisable to less experienced endoscopists. The study took place in Italy and so participants might be reasonably similar to those who would receive this intervention in the UK. |

**Paggi et al. 20129**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | **Participants** | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Assessment of NBI within a ‘resect and discard’ strategy in routine clinical practice for small polyps (<10 mm) on the accuracy of predicting post-polypectomy surveillance timing.  **First author:** Paggi et al.  **Publication year:** 2012  **Country:** Italy  **Study design:** Prospective cohort study  **Number of centres:** 1 (community hospital)  **Funding:** None reported  **Competing interests:** None | **Index test:** NBI. Highdefinition colonoscopes without additional magnification (HDTV Olympus 180 Exera; Olympus, Tokyo, Japan).  After cecal intubation, the colonic mucosa was evaluated under white light during scope withdrawal and polyp size, location and morphology was documented (the size was estimated by comparison with an open biopsy forceps or the sheath of a polypectomy snare placed against the polyp). Polys identified under white light were further evaluated by NBI and categorised as adenoma or non-adenoma.  **Reference standard:**  Histopathology (assessed by two pathologists, one resident and one senior pathologist with long-standing experience in gastrointestinal pathology) | | | | **Number of participants:** 286 included in analysis (851 patients eligible of which 565 patients were excluded: 351 without polyps, 166 polyps ≥10 mm or cancer, 2 failed polyp retrieval, 46 low confidence NBI evaluation)  **Sample attrition/dropout:** no dropouts reported  **Selection of participants:** Consecutive adult outpatients undergoing colonoscopy for routine clinical indications  **Inclusion criteria for study entry:** routine clinical indications for colonoscopy (screening, surveillance or symptoms) and at least 1 small polyp (<10 mm)  **Exclusion criteria for study entry:**   * Surveillance interval not necessarily directed by endoscopic findings (history of colorectal cancer, inflammatory bowel disease, hereditary polyposis syndromes, hereditary non-polyposis colorectal cancer); * Colonoscopy was performed without NBI technology; * At least one lesion >10 mm or <10 mm and morphologic features suspicious for malignancy (depressed or ulcerated lesions) was detected; * Bowel preparation was inadequate (Aronchick score 4, more than 10% of mucosa not visualised); * Cecal intubation was not accomplished; * Polyps could not be resected due to ongoing anticoagulation or could not be retrieved for pathologic assessment. | | | **Primary outcome of study:** not stated  **Other relevant outcomes:** sensitivity, specificity, positive and negative likelihood ratios, of NBI for adenoma diagnosis in small an diminutive polyps, and left-sided polyps;  Accordance between endoscopy- and histology-directed surveillance strategies after polyp resection.  Subgroup analysis (pre-defined): operative characteristics of NBI for diminutive (≤5 mm) and left-sided (distal to splenic colonic flexure) polyps or the accordance between endoscopy-and histology- directed surveillance strategies for patients with diminutive polyps only.  **Recruitment dates:** February to May or June 2011 (there is a discrepancy in the reporting of the recruitment period in the paper) | |
| **Participant characteristics are reported for the total sample (n=286 with 511 small polyps). Participant characteristics for the subgroup of 197 participants with 399 diminutive polyps are not reported.** | | | | | | | | | |
| **Age, years, mean (SD)** | | | 60.3 (16.2) | | | | | | |
| **Other key patient characteristics** | | | Male, n (%): 160 (55.9) | | | | | | |
|  | | | First degree colorectal cancer family history, n (%): 44 (15.4) | | | | | | |
|  | | | Indication for colonoscopy, n (%) | | | | | | |
|  | | | Screening: 107 (37.4) | | | | | | |
|  | | | Surveillance: 75 (26.2) | | | | | | |
|  | | | Symptoms: 104 (36.4) | | | | | | |
| **Endoscopist experience and training** | | | | | 6 highly experienced staff endoscopists, who regularly practiced NBI technology (which was current practice at the Division of Gastroenterology where this study too place since 2009). All endoscopists underwent a re-training session with pro- and post-test assessments of a slide set of endoscopic pictures in order to standardise the classification of adenomatous and hyperplastic lesions prior to the start of the study. | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | | | | Each small polyp was categorised as adenoma or non-adenoma according to simplified NBI criteria as proposed by Rex et al. (13) and summarised below.   |  |  | | --- | --- | | **Predictive of adenomatous polyp** | **Predictive of hyperplastic polyp** | | * Overall brown colour * Short, thick blood vessel * Tubular or oval pits, variable-size pits | * Bland, featureless appearance * Pattern of black dots surrounded by white * Thin blood vessels coursing across the polyp surface and not surrounding pits | | * Central brown depression |  | | * Straight blood vessels around pits forming rectangles, pentagons and so forth |  | | | | | |
| **Sample size calculation** | | | | | Stated that given that the accuracy of histology in differentiating adenomas from non-adenomas is reported to range from 85% to 95% (reference provided in the paper) and that NBI could be competitive if reaching an accuracy of at least 90%, as sample size of 508 polyps was required – 511 small polyps were identified. | | | | |
| **Results (all high confidence characterisations)** | | | | | | | | | |
| **Subgroup: diminutive polyps (n=197)** | | **Adenomatous polyps on histopathology** | | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | | (a) 233 | | | | (b) 48 | | | 281 |
| **Index test negative** | | (c) 161 | | | | (d) 102 | | | 118 |
| **Total** | | 249 | | | | 150 | | | 399 |
| **Accuracy ([a+d]/[a+b+c+d])** | | 84.0% (CI not reported and not calculated by reviewer) | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 93.9% | 89.77% to 96.28%\* | | |
| **Clinical specificity d / (b + d)** | | | | | | 68.0% | 59.90% to 75.37%\* | | |
| **PPV a / (a + b)** | | | | | | 82.9%\* | 78.00% to 87.13%\* | | |
| **NPV d / (c + d)** | | | | | | 86.4%\* | 78.92% to 92.05%\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 2.93 | 2.31 to 3.70\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.09 | 0.06 to 0.15\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 30.945\* | 16.784 to 57.054\* | | |
| Comments: \* Calculated by reviewer.  Calculations agree with values reported in paper, (although approximation of rounding differs).  1 no advanced adenomas. | | | | | | | | | |
|  | | | | | | | | | |
| **Interpretability of test** | | | | Not reported | | | | | |
| **Inter-observer agreement** | | | | Not reported | | | | | |
| **Intra-observer agreement** | | | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | | | Not reported | | | | | |
| **Adverse events** | | | | Not reported | | | | | |
| **High confidence optical diagnosis** | | | | Endoscopist defined the confidence level of the prediction (high vs low) of polyp diagnosis. Patients with at least one polyp classified as low confidence were not included in the analysis. | | | | | |
| **Low confidence optical diagnosis** | | | | 46 (13.9%) patients were excluded from analysis for having at least one polyp categorised with low confidence by the endoscopist. | | | | | |
| **Number of polyps designated to be left in place** | | | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | Not reported | | | | | |
| **Recommended surveillance interval** | | | | Post- polypectomy surveillance interval on the basis of the number of polyps categorised as adenomas by NBI was assigned by the endoscopist after completion of the colonoscopy.   * Patients with ≥1 polyps categorised as no adenoma were not given a specific follow-up indication (return to screening colonoscopy at 10 years). * 1 or 2 adenomas, colonoscopy at 5 years * 3 to 10adenomas, colonoscopy at 3 years * ≥10 adenomas, colonoscopy within 3 years   Post-polypectomy surveillance interval was re-assigned once the pathological report was complete (histology-directed strategy) according the US Multi-Society Task Force on Colorectal Cancer (USMSTF).103  Practice guidelines for post-polypectomy surveillance103   |  |  | | --- | --- | | Patients with only 1 or 2 small (<1 cm) tubular adenomas with only low grade dysplasia (low risk subjects) | 5 – 10  years | | Patients with 3 to 10 adenomas, or any adenoma ≤1 cm, or any adenoma with villous features, or high grade dysplasia (high risk subjects) | 3 years | | Patients who have >10 adenomas | < 3 years | | Patients with small rectal hyperplastic polyps | No follow-up indication |   If based on by NBI endoscopic findings, surveillance would have been delayed in seven patients (4%) with diminutive polys and been too soon in 22 (11%) patients. Overall concordance between endoscopy- and histology-directed surveillance intervals for patients with only diminutive polys occurred in 168/197 (85.3%) patients.  Accordance between endoscopy- and histology-directed post-polypectomy surveillance strategies in patients with diminutive polyps (n=197)   |  |  |  |  | | --- | --- | --- | --- | | Endoscopy-directed surveillance | Histology-directed surveillance | | | | 3 years | 5 years | 10 years | | 3 years | 151 | 33 | 13 | | 5 years | 02 | 1121 | 183 | | 10 years | 02 | 72 | 411 |   1 Overall accordance between endoscopy- histology-directed surveillance intervals  2 Surveillance delayed if advised by NBI endoscopy  3 Surveillance too soon if advised by NBI endoscopy | | | | | |
| **Length of time to perform the colonoscopy** | | | | Not reported | | | | | |
| **Number of outpatient appointments** | | | | Not reported | | | | | |
| **Health related quality of life** | | | | Not reported | | | | | |
| **Colorectal cancer** | | | | Not reported | | | | | |
| **Mortality** | | | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Adult outpatients already undergoing colonoscopy for routine clinical indications, of which around 26% attended for surveillance, 37% for screening and 36% had symptoms. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Each polyp was evaluated by pathologists after histopathology. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Two pathologists evaluated each polyp blindly and openly discussed all cases where discrepancy occurred (standard practice at the Institution) | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | While not specifically stated, there appear to have been no withdrawals. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant publications were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The population sample was based on patients from Italy, who were already undergoing colonoscopy for routine clinical indications (surveillance, symptoms and screening) and it is unclear how representative this sample is of the patient population in the UK, and how similar endoscopists training is compared to training received in the NHS. Study was performed in a single centre by highly experienced endoscopists who used NBI routinely, so the results may not be applicable to a wider range of settings or to less experienced endoscopists. |

**Patel et al.3**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | | **Participants** | **Outcome measures** | | |
| **Condition being diagnosed / detected:**  Whether endoscopists without prior training can, when using NBI and having taken part in standardised training, achieve the American Society for Gastrointestinal Endoscopy (ASGE) PIVI thresholds for characterising diminutive polyps with high confidence: NPV ≥90% for adenomas in the rectosigmoid and a ≥90% agreement in surveillance intervals, compared with histopathology.  **First author:** Patel et al  **Publication year:** 2016  **Country:** USA  **Study design:** Prospective cohort.  **Number of centres:** 4 [two tertiary academic medical centres (University of Michigan and University of Colorado) and two Veterans Affairs hospitals (Ann Arbor VA and Denver VA)]  **Funding:**  American Society for Gastrointestinal Endoscopy Quality in Endoscopic Research Award.  **Competing interests:**  Two authors reported conflicts of interest. One was a consultant for and received a research grant from Olympus America. The other was supported by funding from the University of Colorado, Department of Medicine outstanding early scholars program, AGA-Takeda Research Scholars Award in Barrett’s Esophagus and Gastroesophageal Reflux Disease, educational grants from Covidien and Cook, and was a consultant for Covidien. The other authors reported that they had no conflicts. | **Index test:**  NBI. The academic medical centres used Evis Exera II CV-180 processors with CF-H180AL and PCF-H180AL colonoscopes. The Veterans Affairs centres used Evis Exera III CV-190 processors and CF-H190AL and PCF-H190AL colonoscopes (Olympus America). HD monitors were used for all the colonoscopies.  **Reference standard:**  Histopathology | | | | | **Number of participants:**  1451 colonoscopies in which a diminutive polyp was found.  **Sample attrition/dropout:**  Not reported.  **Selection of participants:**  Participants undergoing colonoscopy for any indication between November 2013 and November 2014 and who had at least one diminutive polyp were included in the study. Specific indications not provided, but information on page 408 implies that patients with inflammatory bowel disease and a history of colorectal cancer or familial cancer syndrome may have been included. Information in Table 2, page 410, suggests that the study included 6 patients with familial syndrome and 3 with a history of inflammatory bowel disease.  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  Not stated. | **Primary outcome of study:**  Whether the endoscopists could achieve the PIVI thresholds for characterising diminutive polyps with high confidence: NPV ≥90% for adenomas in the rectosigmoid and a ≥90% agreement in surveillance intervals, compared with histopathology.  **Other relevant outcomes:**  Accuracy, sensitivity and NPV for characterising diminutive polyps using NBI by level of confidence and polyp location.  **Recruitment dates:**  Endoscopist training took place in October 2013. Study recruitment took place between November 2013 and November 2014. | | |
| **Participant characteristics** | | | | | | | | | |
| **Age, years, mean (SD)** | Not reported. | | | | | | | | |
| **Other key patient characteristics (list)** | 3012 diminutive polyps were included in the study, identified from 1451 colonoscopies. 1088 (36%\*) of the diminutive polyps were located in the rectosigmoid. \*% calculated by reviewer.  Patient characteristics not reported. | | | | | | | | |
| **Endoscopist experience and training** | 26 endoscopists performed the colonoscopies. The endoscopists had no prior training in NBI and took part in a standardised training session at the start of the study in NBI interpretation, with structured performance feedback throughout the duration of the study.  The training session lasted approximately two hours. The endoscopists viewed a 20-min audiovisual tool designed by one of the study authors, which described established NBI criteria for characterising polyps. They then viewed 80 videos of diminutive polyps taken when using high-definition white light and NBI. They predicted each polyp’s histology and recorded their confidence in their judgement (high or low). Then the histopathological diagnosis was revealed and the endoscopists received feedback where there was not consensus.  The endoscopists who completed this session then took part in a “study orientation” and were introduced to the ‘characterise, resect, and discard’ strategy, the proposed PIVI thresholds and definitions of high and low confidence predictions.  Endoscopists who had annually performed <200 colonoscopies were excluded from the study. 57.7% of the endoscopists who took part in the study reported performing between 201 and 500 colonoscopies per year and the other participants reported performing >500 colonoscopies per year. 8 (30.8%) had less than 5 years’ experience, 10 (38.5%) had 5-10 years’ experience, 4 (15.4%) had 11-20 years’ experience), and 4 (15.4%) had more than 20 years’ experience. | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | States used previously established NBI criteria and cites 3 references by Rastogi et al.:  74  86  87  Sessile serrated polyps were analysed as non-adenomas. | | | | | | | | |
| **Sample size calculation** | It was calculated that approximately 2727 polyps and 1364 colonoscopies were needed to detect an NPV ≥90%, assuming that the true NPV would be 95% for rectosigmoid polyps characterised with high confidence. Calculations were based on an expected requirement of “336 total rectostigmoid nonadenomatous polyps characterised with high confidence … [and] 2 polyps per colonoscopy, 22% of all diminutive polyps located in the rectosigmoid, 70% with high confidence and 80% nonadenomas.” (p. 408). | | | | | | | | |
| **Results –** Patel et al. report 9 sets of diagnostic performance data (for 3 areas: all, proximal to the rectosigmoid, rectosigmoid, with an overall result for each region as well as results for high confidence and low confidence characterisations). The reviewer has attempted to impute 2x2 table data to achieve the reported results but it has not been possible to do this and match all the reported outcomes within a set of data. It has also not been possible to find values that are consistent between data sets (i.e. the 2x2 table values for high and low confidence assessments should sum to the 2x2 table for the overall results). Due to the large size of this study illustrative 2x2 tables have been provided for possible use with meta-analysis for the overall dataset, and for high confidence assessments. A 2x2 table has also been imputed for the smallest data set (n = 238, low confidence decisions in the rectosigmoid). | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps identified (n = 2876\*)** | | | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | | | **Hyperplastic polyps on histopathology** | **Total** | | |
| **Index test positive** | (a) 1523\*\* | | | | | (b) 490\*\* | 2013\*\* | | |
| **Index test negative** | (c) 77\*\* | | | | | (d) 786\*\* | 863\*\* | | |
| **Total** | 1600\*\* | | | | | 1276\*\* | 2876 | | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 76.7% (95% CI: 75.2% to 78.3%) | | | | | | | | |
| ***Diagnosis*** | | | **Value** | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | 95.2% | | | | 92.6% to 97.8% | | |
| **Clinical specificity d / (b + d)** | | | 61.6% | | | | 55.8% to 67.4% | | |
| **PPV a / (a + b)** | | | 77.9% | | | | 74.2% to 81.6% | | |
| **NPV d / (c + d)** | | | 94.2% | | | | 90.4% to 98.0% | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | Not reported | | | | Not reported | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | Not reported | | | | Not reported | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | Not reported | | | | Not reported | | |
| Comments: Reviewer unable to find a solution for the 2x2 table that satisfies all the reported values. The values provided should be regarded as illustrative only because they produced the reported sensitivity and specificity, the values for PPV and NPV are lower than reported (75.7% and 91.1%, respectively) whilst the accuracy is higher than reported (80.3%). As the reviewer is not confident in the solution for the 2x2 table these values have not been used to calculate positive and negative likelihood ratios or the diagnostic odds ratio.  \* Polyps were missing from the analysis if a confidence level had not been assigned or if histology was missing, “other” (p. 411), or if the polyp could not be retrieved.  \*\* Calculated by the reviewer | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps identified that were proximal to the rectosigmoid (n = 1818)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 1818 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 78.8% (95% CI: 75.5% to 82.0%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 91.0% | | | | | 88.3% to 94.0% |
| **Clinical specificity d / (b + d)** | | | | 36.9% | | | | | 27.7% to 46.1% |
| **PPV a / (a + b)** | | | | 83.5% | | | | | 79.4% to 87.6% |
| **NPV d / (c + d)** | | | | 65.6% | | | | | 59.2% to 71.9% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table as potential solutions did not provide outcomes that matched the reported values and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations.  \* Calculated by the reviewer | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps identified that were located in the rectosigmoid (n = 1058)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 1058 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 80.9% (76.7% to 85.1%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 88.4% | | | | | 84.8% to 92.0% |
| **Clinical specificity d / (b + d)** | | | | 78.3% | | | | | 71.8% to 84.9% |
| **PPV a / (a + b)** | | | | 56.8% | | | | | 51.1% to 62.4% |
| **NPV d / (c + d)** | | | | 93.7% | | | | | 91.8% to 95.7% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations.  Individually 20 of the 26 endoscopists achieved ≥90% NPV in the rectosigmoid. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps where predictions were made with high confidence (n = 2178)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) 1296\* | | | (b) 264\* | | | 1560\* | |
| **Index test negative** | | (c) 32\* | | | (d) 586\* | | | 618\* | |
| **Total** | | 1328\* | | | 850\* | | | 2178 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 84.8% (82.1% to 87.5%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 97.6% | | | | | 95.3% to 99.9% |
| **Clinical specificity d / (b + d)** | | | | 68.9% | | | | | 60.5% to 77.2% |
| **PPV a / (a + b)** | | | | 83.1% | | | | | 79.1% to 87.2% |
| **NPV d / (c + d)** | | | | 98.3% | | | | | 95.7% to 100.0% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer has found a solution for the 2x2 table that provides the sensitivity, specificity and PPV values reported in the paper. However, the imputed 2x2 values produce a lower NPV (94.8%) in comparison to the value reported in the paper. This solution should be regarded as illustrative. As the reviewer is not confident in the solution for the 2x2 table these values have not been used to calculate positive and negative likelihood ratios or the diagnostic odds ratio.  \* Calculated by the reviewer. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps proximal to the rectosigmoid where predictions were made with high confidence (n = 1360)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 1360 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 84.7% (80.7% to 88.6%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 96.2% | | | | | 94.1% to 98.4% |
| **Clinical specificity d / (b + d)** | | | | 34.9% | | | | | 22.1% to 47.7% |
| **PPV a / (a + b)** | | | | 85.2% | | | | | 80.9% to 89.5% |
| **NPV d / (c + d)** | | | | 77.1% | | | | | 67.9 to 86.2% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps located in the rectosigmoid where predictions were made with high confidence (n = 818)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 818 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 88.1% (83.2% to 92.9%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 90.9% | | | | | 87.4% to 94.4% |
| **Clinical specificity d / (b + d)** | | | | 88.6% | | | | | 81.0% to 96.1% |
| **PPV a / (a + b)** | | | | 65.7% | | | | | 60.9% to 70.6% |
| **NPV d / (c + d)** | | | | 94.7% | | | | | 92.6% to 96.8% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps where predictions were made with low confidence (n = 694)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 694 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 60.2% (55.4% to 65.1%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 74.6% | | | | | 65.9% to 83.4% |
| **Clinical specificity d / (b + d)** | | | | 50.6% | | | | | 45.6% to 55.7% |
| **PPV a / (a + b)** | | | | 55.3% | | | | | 45.6% to 64.9% |
| **NPV d / (c + d)** | | | | 80.8% | | | | | 67.9% to 93.7% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps proximal to the rectosigmoid where predictions were made with low confidence (n = 456)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) Incalculable | | | (b) Incalculable | | | a+b | |
| **Index test negative** | | (c) Incalculable | | | (d) Incalculable | | | c+d | |
| **Total** | | a+c | | | b+d | | | 456 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 61.3% (54.3% to 68.4%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 73.7% | | | | | 65.8% to 81.5% |
| **Clinical specificity d / (b + d)** | | | | 44.4% | | | | | 37.3% to 51.1% |
| **PPV a / (a + b)** | | | | 72.9% | | | | | 60.2% to 85.6% |
| **NPV d / (c + d)** | | | | 54.2% | | | | | 44.1% to 64.3% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer unable to impute data for 2x2 table and therefore could not check if sensitivity etc values reported in the paper match the reviewer’s calculations. | | | | | | | | | |
| **Results – NBI for characterising all diminutive polyps located in the rectosigmoid where predictions were made with low confidence (n = 238)** | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** | |
| **Index test positive** | | (a) 34 | | | (b) 81 | | | 115 | |
| **Index test negative** | | (c) 12 | | | (d) 111 | | | 123 | |
| **Total** | | 46 | | | 192 | | | 238 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 60.5% (52.5% to 68.5%) | | | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 73.9% | | | | | 61.2% to 86.6% |
| **Clinical specificity d / (b + d)** | | | | 57.8% | | | | | 46.9% to 68.8% |
| **PPV a / (a + b)** | | | | 29.1% | | | | | 20.8% to 37.3% |
| **NPV d / (c + d)** | | | | 90.1% | | | | | 84.8% to 95.4% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | Not reported | | | | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | Not reported | | | | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | Not reported | | | | | Not reported |
| Comments: Reviewer has imputed data for 2x2 table which broadly produces the same sensitivity etc values as reported in the paper. | | | | | | | | | |
| **Inter-observer agreement** | | | Not reported. | | | | | | |
| **Intra-observer agreement** | | | Not reported. | | | | | | |
| **Test acceptability (patients / clinicians)** | | | Not reported. | | | | | | |
| **Adverse events** | | | Not reported. | | | | | | |
| **High confidence optical diagnosis** | | | 74.3% (n = 2293) of the diminutive polyp predictions were made with high confidence.  74.4% (n = 844) of the diminutive polyp predictions of those in the rectosigmoid were made with high confidence. | | | | | | |
| **Low confidence optical diagnosis** | | | 24.3% (n = 731) of the diminutive polyp predictions were made with low confidence. NB a classification of high or low confidence was missing for 1.4% (n = 42) of the diminutive polyps.  22.1% (n = 251) of the diminutive polyp predictions of those in the rectosigmoid were made with low confidence. | | | | | | |
| **Number of polyps designated to be left in place** | | | Not reported. | | | | | | |
| **Number of polyps designated to be resected and discarded** | | | Not reported. | | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | Not reported. | | | | | | |
| **Recommended surveillance interval** | | | The following guidelines were used to determine surveillance intervals: Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012; 143:844-857. The surveillance interval prediction was based on NBI predictions combined with histology outcome for low confidence and >5mm polyps.  There was a 91.2% (95% CI: 89.67% to 92.65%; 1279 of 1403) agreement in surveillance intervals when using NBI to characterise polyps with high confidence in combination with histopathology for low confidence characterisations and polyps >5mm.  There was a disagreement in surveillance interval in 124 colonoscopies. In 31.5% (n = 39) of these cases, endoscopists using NBI predicted a longer interval than histopathology. In 66.1% (n = 82) of these cases, endoscopists predicted a shorter interval than histopathology.  Overall, 97.0% ([1279 + 82] / 1403) of the endoscopists’ predictions would bring patients back on time or early for surveillance follow-up examination.  NB Endoscopists only made surveillance interval predictions for high confidence diminutive polyps. If there were 1 or 2 low confidence characterisations, endoscopists were asked to predict the surveillance interval based on all the possible histologic outcomes for the low confidence characterisations. A surveillance interval prediction was not made if there were more than two low confidence predictions. Also, they did not predict surveillance intervals if there were >10 polyps or if there was a reason to deviate from standard polyp surveillance guidelines (e.g. if a patient had inflammatory bowel disease) or if the endoscopist was unable to retrieve all the polyps removed. | | | | | | |
| **Length of time to perform the colonoscopy** | | | Not reported. | | | | | | |
| **Number of outpatient appointments** | | | Not reported. | | | | | | |
| **Health related quality of life** | | | Not reported. | | | | | | |
| **Colorectal cancer** | | | Not reported. | | | | | | |
| **Mortality** | | | Not reported. | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | This was a large study of 1451 colonoscopies, but no details were provided about the participants and the specific indications for carrying out the procedure. | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | The reference standard was histopathology, the gold standard. | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The investigators aimed to verify all polyps with histopathology. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | The index test result did not influence whether or not a polyp was resected and sent for histopathological assessment. | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The pathologists were blinded to study participation and NBI polyp prediction. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histopathological assessment was subsequent to the index test with NBI. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Authors have reported that polyps were excluded from the analysis if a confidence level was not assigned or if histology was missing, “other” (p. 411), or if the polyp could not be retrieved. | Yes |
| 11 | Were withdrawals from the study explained? | Unclear if there were any withdrawals from the study, as the authors do not report this nor the number of participants selected to take part and the number of participants included in the data analyses. | Unclear |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional relevant studies identified. |

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| Summary reviewer’s comments |
| This was a large study of 1451 colonoscopies that were carried out by 26 endoscopists with varying levels of experience in carry out colonoscopies, but no prior training in NBI. The endoscopists were trained in NBI as part of the study. The findings may therefore be applicable to endoscopists of varying professional experience but with little training in NBI. The patient indications for colonoscopy were unclear and therefore it is unclear to which patient populations the findings of the study might generalise, but it is likely, given the large number of colonoscopies carried out, that a broad spectrum of patients were included. |

**Pigo et al.81**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | **Outcome measures** |
| **Condition being diagnosed / detected:**  Use of high-definition white light (HDWL) i-scan for diagnosing the histology of colorectal polyps. Part of study aim was to also examine inter- and intra-observer agreement regarding the histological diagnoses.  One endoscopist carried out a real-time assessment of all patients. Four other endoscopists then carried out a blinded assessment using only pictures generated from the colonoscopy to assess inter-observer agreement. After six months, another assessment was carried out by these same four endoscopists to assess intra-observer agreement.  **First author:** Pigò et al  **Publication year:** 2013  **Country:** Italy  **Study design:** Prospective cohort  **Number of centres:** 1 (a hospital)  **Funding:** Not reported  **Competing interests:** Not reported | **Index test:**  Endoscopists used HDWL i–scan to predict the histology of colorectal polyps in real-time. EPK-*i* processor, HD colonoscope EC-3890*i*. 190-inch SXGA monitor. Surface enhancement SE4+ and TE-p or TE-c mode used (Tone Enhancement for colonic lesions).  **Reference standard:**  Histopathology | | **Number of participants:** 78  **Sample attrition/dropout:**  Not reported.  **Selection of participants:**  Consecutive patients, with at least one colorectal polyp, who met the inclusion criteria below.  **Inclusion criteria for study entry:**  Undergoing screening colonoscopy for colorectal cancer or for surveillance following polypectomy or colorectal cancer surgery; or, persistent gastrointestinal symptoms.  **Exclusion criteria for study entry:**  < 18 years-old; inflammatory bowel disease, hereditary non-polyposis colorectal cancer, or familial adenomatous polyposis; currently using antiplatet agents or anticoagulants; unable to provide informed consent. | **Primary outcome of study:**  Not stated, though aim of the study is stated as an evaluation of the diagnostic prediction of i-scan.  **Other relevant outcomes:**  Sensitivity, specificity and negative predictive value (NPV) for assessing histology of diminutive polyps located in the rectosigmoid. Accuracy, sensitivity and sensitivity also reported for assessment of all polyps, regardless of size. Inter- and intra-observer agreement reported, but was based on still picture evaluations rather than real-time assessment (so not data extracted).  **Recruitment dates:**  February to May 2011 |
| **Participant characteristics** | | | | |
| **Age, years, mean (SD)** | 52 (9) | | | |
| **Other key patient characteristics (list)** | Gender: male n=40 (51.3%); female n=38 (48.7%). [% calculated by reviewer.]  Indications for colonoscopy, n/N (%): positive faecal occult blood test: 51/78 (65.4%); polypectomy follow-up: 20/78 (25.6%); gastrointestinal symptoms: 7/78 (9.0%); colorectal cancer familiarity: 9/78 (11.5%). [%s calculated by reviewer.]  Total number of polyps assessed: 150  Lesion size, n (%) polyps: ≤5mm: 88 (58.7%); >5mm: 62 (41.3%). [%s calculated by reviewer.] Mean polyp size 6.8mm (SD 5.5), median polyp size 5mm (2-30).  Note: Authors report diagnostic accuracy results (i.e. sensitivity, specificity and NPV) of real-time assessment of diminutive polyps located in the rectosigmoid only (n = 33 polyps). No other results relating to the assessment of diminutive polyps are reported. | | | |
| **Endoscopist experience and training** | The endoscopist who carried out all the first assessments had a history of undertaking >1,000 colonoscopies per year (although number of years of experience are not provided). No details about the endoscopist’s training or experience in using i-scan are reported. | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Paris Classification and NBI International Colorectal Endoscopic Classification. | | | |
| **Sample size calculation** | Not reported. | | | |
| **Results: i-scan – assessment of diminutive polyps located in the rectosigmoid (n = 33 polyps)** | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | **Total** |
| **Index test positive** | (a) 17\* | | (b) 2\* | 19\* |
| **Index test negative** | (c) 1\* | | (d) 13\* | 14\* |
| **Total** | 18\* | | 15\* | 33\* |
| **Accuracy** ([a+d]/[a+b+c+d]) | 91%\* (30 of 33 polyps accurately diagnosed) | | | |
| ***Diagnosis: i-scan – assessment of diminutive polyps located in the rectosigmoid (n = 33 polyps)*** | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 94% | | 83% to 100% |
| **Clinical specificity d / (b + d)** | | 87% | | 72% to 100% |
| **PPV a / (a + b)** | | 89%\* | | 67% to 99%\* |
| **NPV d / (c + d)** | | 93% | | 81% to 100% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 7.08\* | | 1.94 to 25.86\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.06\* | | 0.01 to 0.44\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 110.500\* | | 9.01 to 1355.244\* |
| \* Calculated by reviewer | | | | |
| **Interpretability of test** | |  | | |
| **Inter-observer agreement** | | Inter-observer agreement was calculated for the assessment of diminutive polyps, but was based on endoscopists’ assessments of still images rather than real-time assessment. Data therefore not extracted. | | |
| **Intra-observer agreement** | | Intra-observer agreement assessed based on endoscopists’ assessment of still images rather than real-time assessment. Authors do not report intra-observer agreement for the evaluation of diminutive polyps. Data therefore not extracted. | | |
| **Test acceptability (patients / clinicians)** | | Not reported. | | |
| **Adverse events** | | Not reported. | | |
| **High confidence optical diagnosis** | | Not reported. | | |
| **Low confidence optical diagnosis** | | Not reported. | | |
| **Number of polyps designated to be left in place** | | Not reported. | | |
| **Number of polyps designated to be resected and discarded** | | Not reported. | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported. | | |
| **Recommended surveillance interval** | | Not reported. | | |
| **Length of time to perform the colonoscopy** | | Not reported. | | |
| **Number of outpatient appointments** | | Not reported. | | |
| **Health related quality of life** | | Not reported. | | |
| **Colorectal cancer** | | Not reported. | | |
| **Mortality** | | Not reported. | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | The study included patients undergoing screening or surveillance colonoscopy and patients with persistent gastrointestinal symptoms suggestive of colorectal cancer. The study excluded patients with inflammatory bowel disease, hereditary non-polyposis colorectal cancer, or familial adenomatous polyposis. The patient population is therefore relevant to the scope of this appraisal. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Reference standard was histopathology, the gold standard. | Yes |
| 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? | The real-time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis were performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polyps removed were sent for histological examination. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All polyps removed were sent for histological examination. | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? | Virtual chromoendoscopy and histopathology were performed separately. | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | The pathologist who carried out the histopathology assessment was blinded to the endoscopist’s assessment. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Histopathological assessment was subsequent to the index test with i-scan. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Unclear if there were any withdrawals from the study. 78 patients were recruited and 150 polyps were included in the analysis, but the authors do not state if the 150 polyps were from the full sample of 78 recruited participants. | Unclear |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant publications identified. NB Cites paper by Lee (2001), but the date is incorrect and it is Lee (2011), which we have already identified through our searches. |

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| Summary reviewer’s comments |
| The majority of patients had been screened for bowel cancer and had a positive fecal occult blood test. These results were obtained from an endoscopist who was experienced in carrying out colonoscopies, but no details were provided about the endoscopist’s experience or training in using i-scan. The study took place in one hospital in Italy. The results may therefore not be applicable to endoscopists with a differing level of experience and/or training working in other settings and/or countries. |

**Pohl et al.10**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | **Participants** | | | **Outcome measures** |
| **Condition being diagnosed / detected:**  Diagnosis of whether polyps were adenomas or not. Aim of study was to examine factors related to the quality of optical diagnosis of diminutive polyps using NBI.  **First author:**  Pohl et al.  **Publication year:** 2016  **Country:** USA  **Study design:**  Prospective cohort – participants who had previously taken part in a two-arm RCT were analysed as one group in this study. In the RCT, participants had been randomised to either cap-assisted or standard colonscopy.  **Number of centres:**  2 (academic medical centres)  **Funding:**  Not reported.  **Competing interests:**  None. | **Index test:**  NBI. High definition colonoscopes were used (models H-CF 180 or H-PCF 180, Olympus Inc., USA). Participants underwent either cap-assisted colonoscopy (4-mm Olympus cap) or standard colonoscopy. Whether magnification was used or not was not reported. Polyps were examined with white light and NBI.  Endoscopists rated their level of confidence in their prediction of polyp histology as high, low or don’t know.  **Reference standard:**  Histopathology. | | | **Number of participants:**  1100 participants were eligible. 607 participants had at least one polyp; 566 participants had at least one diminutive polyp.  **Sample attrition/dropout:**  Of the 1113 participants randomised to the original RCT, 13 did not undergo optical diagnosis and so were not included in the prospective cohort study.  **Selection of participants:**  See inclusion and exclusion criteria below.  **Inclusion criteria for study entry:**  Patients aged 50-89 years, presenting for an outpatient colonoscopy.  **Exclusion criteria for study entry:**  Patients with inflammatory bowel disease, a coagulopathy, or with an American Society of Anesthesiologists (ASA) class > 3. Patients who did not undergo real-time assessment were also excluded. | | | **Primary outcome of study:**  The following outcomes were described as the “main” outcomes of the study in the abstract:  Negative predictive value (NPV) for diminutive polyps diagnosed as adenomas in the rectosigmoid (stated later in the paper that this was to assess if the Preservation and Incorporation of Valuable endoscopic Innovations [PIVI] quality benchmark of at least 90% could be met); and, assessment of the endoscopist-related and procedural factors associated with the quality of optical diagnosis – the NPV for diminutive adenomas in the rectosigmoid colon and the concordance of surveillance intervals (effect of endoscopists’ prior experience data extracted but findings for three other procedural factors investigated not data extracted).  **Other relevant outcomes:**  Surveillance intervals - study also assessed the concordance of optical diagnosis surveillance recommendations with those from histopathology according to the PIVI benchmark of 90%; sensitivity; specificity; and positive predictive value (PPV).  **Recruitment dates:**  Not reported |
| **Participant characteristics** | | | | | | | |
| **Age, years, mean (SD)** | 61.8 (8.4) | | | | | | |
| **Other key patient characteristics (list)** | The 607 patients had a total of 1650 polyps, of which 1311 (79%) were diminutive (defined as 1-5mm). Location of all polyps also reported but not data extracted. Of the 1650 polyps identified, 42 (2.6%) were not diagnosed, due to either not being retrieved or there being insufficient material to make a diagnosis.  Characteristics of the 1100 eligible participants (characteristics for the 607 participants with polyps not reported):  Gender, n (%): male 702 (63.8); female 398 (36.2).  Indications, n (%): screening 580 (52.7); surveillance 332 (30.2); bleeding, anemia, +FOBT 97 (8.8); other 91 (8.3). | | | | | | |
| **Endoscopist experience and training** | 10 endoscopists carried out the colonoscopies. None had had prior experience (beyond application of NBI in routine endoscopy practice) of optical diagnosis (although almost all had extensive colonoscopy experience), but two had been involved in other clinical studies on endoscopic imaging technologies. All the endoscopists took part in an NBI training course at the start of the study. Training was repeated when the study reached 50% of the enrolment target. The training course followed the structure of a validated programme published before the NBI International Colorectal Endoscopic (NICE) classification was available (reference provided). The content of the training included a pretest, a didactic session, and a post-test. The course took one-hour and was delivered to a group, enabling interaction and immediate feedback. As part of the training, the endoscopists also all had access at their units to a reference book containing images summarising all the polyp cases covered in the training. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | During real-time diagnosis, polyps were classified as adenomatous or non-adenomatous based on colour, the appearance of vessels, and mucosal pattern.90 No formal method was used for evaluating sessile serrated polyps/adenomas (SSP/A). If an endoscopist suspected that a polyp was a SSP/A, they categorised it as a neoplastic polyp.  During histopathology, polyps were classified as neoplastic and non-neoplastic. All adenomatous and SSP/As were classified as neoplastic, based on the Wold Health Organisation classification of serrated polyps.147 4.3% of polyps were SSP/As. All other polyps were classified as neoplastic. | | | | | | |
| **Sample size calculation** | The sample size needed for the original RCT was calculated to be 1100 participants. It was expected that 45% of the participants would have a polyp and would therefore be included in the post-polypectomy surveillance interval analysis. Based on a surveillance interval recommendation concordance of at least 93%, it was expected that this sample size would provide a 95% CI with the lower margin above 90% (90.4% to 95.1%). | | | | | | |
| **Results – polyps sized 1-5mm diagnosed with high confidence** | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 408 | | | (b) 77\* | | | 485 |
| **Index test negative** | (c) 84\* | | | (d) 391\* | | | 475\* |
| **Total** | 492 | | | 468\* | | | 960 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 83.2% (799\* of 960 polyps correctly classified) | | | | | | |
| ***Diagnosis*** | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | 83% | | | 79.30% to 86.15%\* | |
| **Clinical specificity d / (b + d)** | | | 84% | | | 79.87% to 86.79%\* | |
| **PPV a / (a + b)** | | | 84.1% | | | 80.56% to 87.26%\* | |
| **NPV d / (c + d)** | | | 82.3% | | | 78.58% to 85.64%\* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | 5.04\* | | | 4.09 to 6.21\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | 0.20\* | | | 0.17 to 0.25\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | 24.664\* | | | 17.574 to 34.614\* | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV match the values reported in the paper. Paper did not report CIs.  \* Calculated by reviewer. | | | | | | | |
| **Results – polyps sized 1-5mm located in the proximal colon diagnosed with high confidence** | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 262 | | | (b) 26\* | | | 288 |
| **Index test negative** | (c) 56\* | | | (d) 43\* | | | 99\* |
| **Total** | 318 | | | 69\* | | | 387 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 78.8% (305\* of 387 polyps correctly classified) | | | | | | |
| ***Diagnosis*** | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | 82% | | | 77.75% to 86.41%\* | |
| **Clinical specificity d / (b + d)** | | | 62% | | | 49.83% to 73.71%\* | |
| **PPV a / (a + b)** | | | 91.0% | | | 87.05% to 94.02%\* | |
| **NPV d / (c + d)** | | | 43.4% | | | 33.50% to 53.77%\* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | 2.19\* | | | 1.61 to 2.97\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | 0.28\* | | | 0.21 to 0.38\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | 7.738\* | | | 4.393 to 13.627\* | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV match the values reported in the paper. Paper did not report CIs.  \* Calculated by reviewer. | | | | | | | |
| **Results – polyps sized 1-5mm located in the distal colon diagnosed with high confidence** | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 146 | | | (b) 51\* | | | 197 |
| **Index test negative** | (c) 28\* | | | (d) 348\* | | | 376\* |
| **Total** | 174 | | | 399\* | | | 573 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 86.2% (494\* of 573 polyps correctly classified) | | | | | | |
| ***Diagnosis*** | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | 84% | | | 77.59% to 89.03%\* | |
| **Clinical specificity d / (b + d)** | | | 87% | | | 83.54% to 90.33%\* | |
| **PPV a / (a + b)** | | | 74.1% | | | 67.41% to 80.08%\* | |
| **NPV d / (c + d)** | | | 92.6% | | | 89.42% to 94.99%\* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | 6.56\* | | | 5.04 to 8.55\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | 0.18\* | | | 0.13 to 0.26\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | 35.580\* | | | 21.583 to 58.653\* | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV match the values reported in the paper. Paper did not report CIs.  \* Calculated by reviewer. | | | | | | | |
| **Results – polyps sized 1-5mm located in the rectosigmoid diagnosed with high confidence** | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | (a) 101 | | | (b) 44\* | | | 145 |
| **Index test negative** | (c) 17\* | | | (d) 328\* | | | 345\* |
| **Total** | 118 | | | 372\* | | | 490 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 87.6% (429\* of 490 polyps correctly classified) | | | | | | |
| ***Diagnosis*** | | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | | 86% | | | 77.94% to 91.38%\* | |
| **Clinical specificity d / (b + d)** | | | 88% | | | 84.45% to 91.27%\* | |
| **PPV a / (a + b)** | | | 69.7% | | | 61.48% to 77.01%\* | |
| **NPV d / (c + d)** | | | 95.1% | | | 92.23% to 97.10%\* | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | 7.24\* | | | 5.43 to 9.64\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | 0.16\* | | | 0.11 to 0.25\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | 44.289\* | | | 24.245 to 80.902\* | |
| Comments:  Reviewer’s calculations of sensitivity, specificity, PPV and NPV match the values reported in the paper. Paper did not report CIs.  \* Calculated by reviewer. | | | | | | | |
| **Effect of endoscopist prior experience on NPV for rectosigmoid\* diminutive adenomas and the concordance of surveillance recommendations** | | | | | | | |
| Prior experience | | NPV % (95% CI) | | | Surveillance interval concordance % (95% CI) | | |
| Yes (n = 2 endoscopists) | | 96.6 (92.7 to 98.7) | | | 94.4 (90.2 to 97.2) | | |
| No (n = 8 endoscopists) | | 93.5 (88.7 to 96.7) | | | 92.4 (89.2 to 94.9) | | |
| Comments:  Two endoscopists had prior experience and research interest in image-enhanced endoscopy. The eight endoscopists without prior experience had only experience of NBI in routine endoscopy practice.  \* The Methods and Results sections of the paper state that NPV was for rectosigmoid diminutive adenomas, but where these results are reported in Table 5 in the paper, the associated diminutive polyp n = 960. Reviewer notes that elsewhere in the paper, it is reported that there were 490 diminutive polyps diagnosed with high confidence located in the rectosigmoid and a total of 960 diminutive polyps diagnosed with high confidence located in the proximal and distal colon. It is therefore possible that the reported NPVs could relate to polyps in the distal and proximal colon rather than the rectosigmoid, but this is not clear. | | | | | | | |
| **Interpretability of test** | | | Not reported | | | | |
| **Inter-observer agreement** | | | Not reported | | | | |
| **Intra-observer agreement** | | | Not reported | | | | |
| **Test acceptability (patients / clinicians)** | | | Not reported | | | | |
| **Adverse events** | | | Not reported | | | | |
| **High confidence optical diagnosis** | | | 960 of the 1311 (73.2%\*) diminutive polyps (sized 1-5mm) were diagnosed with high confidence. (\*% calculated by reviewer.) | | | | |
| **Low confidence optical diagnosis** | | | Not reported | | | | |
| **Number of polyps designated to be left in place** | | | Not reported | | | | |
| **Number of polyps designated to be resected and discarded** | | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | Not reported | | | | |
| **Recommended surveillance interval** | | | Study used two methods to determine surveillance intervals: 1) combining results from high confidence optical diagnosis of diminutive polyps with histopathology results for all other polyps, and 2) based solely on histopathology for all polyps. The US multi-society taskforce guidelines102,104 were used to assign surveillance intervals.  Among all patients who had a colonoscopy, the optical diagnosis assigned surveillance interval agreed with that of histopathology in 96% of the participants. Among the 566 participants with at least one diminutive polyp the surveillance interval assigned with optical diagnosis agreed with the interval assigned by histopathology in 93% of patients. In 24 cases the optical diagnosis assigned surveillance interval was shorter than the one assigned by histopathology. In 15 cases it was longer. Eight of the 10 endoscopists reached the 90% PIVI threshold.  Surveillance intervals concordance according to endoscopist experience is data extracted above under ‘Effect of endoscopist prior experience on NPV for rectosigmoid diminutive adenomas and the concordance of surveillance recommendations’ | | | | |
| **Length of time to perform the colonoscopy** | | | Not reported | | | | |
| **Number of outpatient appointments** | | | Not reported | | | | |
| **Health related quality of life** | | | Not reported | | | | |
| **Colorectal cancer** | | | Not reported | | | | |
| **Mortality** | | | Not reported | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Participants were undergoing surveillance and screening colonoscopy, and colonoscopy to investigate symptoms and a +FOBT. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Whole sample (where polyps could be retrieved/were materially sufficient enough to diagnose). | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Unclear if the pathologists were blinded to the NBI diagnosis. | Unclear |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | The authors did not report the number of polyps identified by NBI that could not be optically diagnosed. (The authors did report those that could not be retrieved or had insufficient material for a histopathological diagnosis.) | No |
| 11 | Were withdrawals from the study explained? | 1113 participants were randomised in the original trial, of whom 13 were not included in this cohort study as they did not undergo optical diagnosis. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant references identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The colonoscopies were performed in this study by 10 endoscopists, in two academic study centres. None of the endoscopists had previous experience of optical diagnosis and all underwent a training session in NBI at the beginning of the study, which was repeated half-way through recruitment to the study. The results may therefore be applicable to endoscopists with relatively little experience of optical diagnosis and NBI. |

**Rath et al.82**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | **Outcome measures** |
| **Condition being diagnosed / detected:** distinguishing hyperplastic from adenomatous distal (located in the descending colon, the sigmoid colon, or the rectum) diminutive polyps  **First author:** Rath et al  **Publication year:** 2015  **Country:** Germany  **Study design:** prospective cohort  **Number of centres:** 1 (Ludwig Demling Endoscopy Center of Excellence at the  University Hospital Erlangen)  **Funding:** Deutsche Forschungsgemeinschaft  (DFG) and Friedrich-Alexander-University Erlangen-Nuremberg (FAU) within the funding programme Open Access Publishing.  Erlangen Interdisciplinary Center for Clinical Research (IZKF). Italian Group for  the study of IBD (IG-IBD)  **Competing interests:** Stated none | **Index test:** real timehigh definition i-Scan (Pentax, Tokyo, Japan) (no information given on model number)  **Reference standard:**  Histopathology | | **Number of participants:** 77  **Sample attrition/dropout:** 224 patients were included, but a sub-group of 77 patients with distal diminutive colorectal polyps (n=121) were analysed. A further sub-group of 59 patients with polyps in the rectosigmoid area is also presented.  **Selection of participants:**  Patients identified during screening or surveillance colonoscopies  **Inclusion criteria for study entry:** as above  **Exclusion criteria for study entry:** history of inflammatory bowel disease, poor bowel preparation, colectomy, anticoagulation or polyposis syndrome. | | **Primary outcome of study:** sensitivity and negative predictive value for prediction of adenomatous  polyp histology according to the PIVI statement  **Other relevant outcomes:**  Diagnostic accuracy,specificity, positive predictive value, surveillance intervals, intraobserver agreement.  **Recruitment dates:** Not stated |
| **Participant characteristics** | | | | | |
| **Age, years, mean (SD)** | 65.5 (14.4) | | | | |
| **Other key patient characteristics (list)** | 49 (63.6%) male, 28 (36.4%) female  Polyp size: ≤ 3mm n=75 (62%); 4-5 mm n=46 (38%); median = 3mm; mean = 3.3. mm  Polyp location: descending colon n=42 (34.7%); sigmoid n=32 (26.5%); rectum n= 47 (38.8%) | | | | |
| **Endoscopist experience and training** | All colonoscopies were performed by a single experienced endoscopist. | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Polyp histology classification based upon previously published and validated criteria, assessing surface characteristics (pit pattern and mucosal vascular pattern morphology, colour, depression) (reference to a published study given). The Paris classification system was also used.  The endoscopist assigned a level of confidence (high or low) to their assessment of each polyp. | | | | |
| **Sample size calculation** | The probability for error (α) was set to 0.05 and the ß-error was set to 0.1 (reflecting a power of 0.90). For white light endoscopy, an expected accuracy of 74 % and for i-scan an expected accuracy of 90 % was assumed [citations are given for previous evaluations of virtual chromoendoscopy], resulting in a calculated sample size of 120 polyps. | | | | |
| **Results** All distal polyps,overall prediction (high and low confidence), n=121 polyps | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology\*** | | **Total** |
| **Index test positive** | (a) 53\*\* | | (b) 11 | | 64\*\* |
| **Index test negative** | (c) 4 | | (d) 52\*\* | | 56\*\* |
| **Total** | 57 | | 63 | | 120 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90.1% (109 of 121 polyps predicted accurately)\*\*\* | | | | |
| ***Diagnosis\*\*\*\**** | | **Value** | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 93.3% | | 82.7%–97.8% | |
| **Clinical specificity d / (b + d)** | | 88.7% | | 77.5%–95% | |
| **PPV a / (a + b)** | | 88.7% | | 77.5%–95% | |
| **NPV d / (c + d)** | | 93.2% | | 82.7%–97.8% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.33 | | 3.10 to 9.15 | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.09 | | 0.03 to 0.22 | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 62.64 | | 18.74 to 209.34 | |
| Comments:  \* 63 polyps were nonadenomatous, of which almost all were hyperplastic by histology (62 out of 63) while 1 polyp was a leiomyoma.  \*\* Calculated by the reviewer.  \*\*\* Reviewer notes that using data provided in the publication, 105 polyps were accurately diagnosed, but the authors state 109 in their accuracy calculations.  \*\*\*\* the sensitivity/specificity, PPV and NPV values here are as reported in the study publication, but they are inconsistent with the values in the 2x2 table above, as reported in the publication. These values give slightly different results (calculated by the reviewers), as follows:  Clinical sensitivity a / (a + c) = 92.98%, 95% CI 83.00% to 98.05%  Clinical specificity d / (b + d) = 82.54%, 95% CI 70.90% to 90.95%  PPV a / (a + b) = 82.81%, 95% CI 71.32% to 91.10%  NPV d / (c + d) = 92.86%, 95% CI 82.71% to 98.02% | | | | | |
| **Results** All distal polyps,high confidence prediction only, n=107 polyps | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | (a) 51\*\*\*\* | | (b) 3\*\*\*\* | | 54\*\*\*\* |
| **Index test negative** | (c) 1\*\*\*\* | | (d) 52\*\*\*\* | | 53\*\*\*\* |
| **Total** | 52\*\*\*\* | | 55\*\*\*\* | | 107 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 103/107 (96.3%) | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 98.1% | | 88.6%–99.9% | |
| **Clinical specificity d / (b + d)** | | 94.4% | | 83.7%–98.6% | |
| **PPV a / (a + b)** | | 94.5% | | 83.9%–98.6% | |
| **NPV d / (c + d)** | | 98.1% | | 88.4%–99.1% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 17.98 \*\*\*\* | | 5.98 to 54.07 \*\*\*\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.02 \*\*\*\* | | 0.00 to 0.14 \*\*\*\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 884.0 \*\*\*\* | | 88.99 to 8781.07 \*\*\*\* | |
| Comments:  \*\*\*\* not reported in the publication, but estimated by the reviewers. The sensitivity/specificity, PPV and NPV values generated by these reviewer estimated values differ slightly from those reported above from the publication, as follows:  Clinical sensitivity a / (a + c) = 98.08%, 95% CI 89.74% to 99.95%  Clinical specificity d / (b + d) = 94.55%, 95% CI 84.88% to 98.86%  PPV a / (a + b) = 94.44%, 95% CI 84.61% to 98.84%  NPV d / (c + d) = 98.11%, 95% CI 89.93% to 99.95% | | | | | |
| **Results** Polyps in the rectosigmoid only, overall prediction(high and low confidence), n=79 polyps | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | NR\*\*\*\*\* | | NR\*\*\*\*\* | | NR\*\*\*\*\* |
| **Index test negative** | NR\*\*\*\*\* | | NR\*\*\*\*\* | | NR\*\*\*\*\* |
| **Total** | 29 | | 50 | | 79 |
| **Accuracy** ([a+d]/[a+b+c+d]) | NR\*\*\*\*\* | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 90.3 % | | 73.1%–97.5% | |
| **Clinical specificity d / (b + d)** | | 87.5 % | | 74.1%–94.8% | |
| **PPV a / (a + b)** | | 82.4 % | | 64.8%–92.6% | |
| **NPV d / (c + d)** | | 93.3 % | | 80.1%–98.3% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | NR | | NR | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | NR | | NR | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | NR | | NR | |
| Comments:  \*\*\*\*\* Data not reported in the study publication, and it was not possible for reviewer to estimate values that match the sensitivity and specificity values reported in the publication. | | | | | |
| **Results** Polyps in the rectosigmoid only(high confidence prediction only), n=72 polyps | | | | | |
|  | **Adenomatous polyps on histopathology** | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | NR\*\*\*\*\* | | NR\*\*\*\*\* | | NR\*\*\*\*\* |
| **Index test negative** | NR\*\*\*\*\* | | NR\*\*\*\*\* | | NR\*\*\*\*\* |
| **Total** | NR\*\*\*\*\* | | NR\*\*\*\*\* | | 72 |
| **Accuracy** ([a+d]/[a+b+c+d]) | NR\*\*\*\*\* | | | | |
| ***Diagnosis*** | |  | |  | |
| **Clinical sensitivity a / (a + c)** | | 96.4 % | | 79.8%–99.8% | |
| **Clinical specificity d / (b + d)** | | 95.5 % | | 83.3%–99.2% | |
| **PPV a / (a + b)** | | 93.1 % | | 75.8%–98.8% | |
| **NPV d / (c + d)** | | 97.7 % | | 86.2%–99.9% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | NR | | NR | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | NR | | NR | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | NR | | NR | |
| Comments  \*\*\*\*\* Data not reported in the study publication, and it was not possible for reviewer to estimate values that match the sensitivity and specificity values reported in the publication. | | | | | |
| **Interpretability of test** | | NR | | | |
| **Inter-observer agreement** | | NA | | | |
| **Intra-observer agreement** | | Intra-observer agreement was achieved in 113 out of 121 polyps (93.4 %). The κ coefficient of agreement was 0.867 [95 % CI: 0.799–0.967] indicating almost perfect agreement. | | | |
| **Test acceptability (patients / clinicians)** | | NR | | | |
| **Adverse events** | | NR | | | |
| **High confidence optical diagnosis** | | A high confidence prediction was made for 107 (88.4%) of the 121 polyps. | | | |
| **Low confidence optical diagnosis** | | A total of 14 (11.6) of the 121 polyps were predicted with low confidence | | | |
| **Number of polyps designated to be left in place** | | NR | | | |
| **Number of polyps designated to be resected and discarded** | | NR | | | |
| **Number of polyps designated for resection and histopathological examination** | | NR | | | |
| **Recommended surveillance interval** | | Surveillance based on European guidelines\*\* was predicted correctly in 69 out of 73 patients (94.5%); agreement was 68 out of 73 patients (93.2%) based on US guidelines\*\*\*. (Surveillance intervals for polyps in the recto-sigmoid area are reported but not extracted here).  Discrepant surveillance intervals between digital chromoendoscopy and histopathology are reported at patient level but not extracted here. Intervals were longer for digital chromoendoscopy.  \*\* European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition–Colonoscopic surveillance following adenoma removal. 2012  \*\*\* Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. 2012 | | | |
| **Length of time to perform the colonoscopy** | | NR | | | |
| **Number of outpatient appointments** | | NR | | | |
| **Health related quality of life** | | NR | | | |
| **Colorectal cancer** | | NR | | | |
| **Mortality** | | NR | | | |

NR = Not reported; NA = Not applicable

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Yes, the study included patients from two of the population groups relevant for this appraisal and who would receive the test in practice (Patients identified during screening or surveillance colonoscopies) | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | Each polyp was assessed by an experienced gastrointestinal pathologist | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Each polyp was assessed by an experienced gastrointestinal pathologist blinded to the real time prediction of polyp histology. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | 224 patients were included in the study, but the analysis included only 77 of these (all were described as having distal diminutive polyps). It is possible that the remaining patients had larger-sized polyps located other than in the distal colon, but this is not explicitly stated. | No |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional relevant studies identified. |

|  |
| --- |
| Summary reviewer’s comments |
| Results reflect the use of i-Scan in what appears to be a specialist endoscopy centre, by a single experienced endoscopist, to characterise diminutive polyps in the distal colon (i.e. descending colon, the sigmoid colon or the rectum) in patients undergoing screening or surveillance colonoscopy. The majority of predictions were made with high confidence. The authors suggest that studies are needed of less experienced and community physicians. |

**Repici et al.11**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Distal diminutive polyps  **First author:** Repici et al  **Publication year:** 2013  **Country:** Italy, Netherlands  **Study design:** Prospective, multicenter study  **Number of centres:** 5  **Funding:** States thatsoftware and web site support were provided by Olympus. No other financial relationships relevant to this publication were disclosed.  **Competing interests:** Not stated, but see ‘Funding’ above. | **Index test:**  Available Olympus  colonoscopes with high-definition and NBI were used in all the centres. Model number not stated. Electronic magnification (x 1.5) was allowed if needed. Polyps were detected with white light and then characterised using NBI  **Reference standard:**  Histopathology | | **Number of participants:** 278  **Sample attrition/dropout:** 212 of 278 patients were included in the analysis of surveillance intervals (patients with at least 1 polyp ≤ 5mm characterised with high confidence) (i.e. for analysis of PIVI surveillance interval agreement threshold of ≥90%). 128/278 patients with polyps ≤ 5mm in the rectosigmoid area assessed with high confidence (i.e. for analysis of PIVI NPV threshold of ≥90%)  **Selection of participants:** Consecutive adult patients referred for elective outpatient colonoscopy (screening, surveillance, or diagnostic workup)  **Inclusion criteria for study entry:** Detection and retrieval for histologic examination at least 1 polyp <10mm.  **Exclusion criteria for study entry:** Previous colon resection; inflammatory  bowel disease; personal history of polyposis syndrome; suspected chronic stricture potentially precluding complete colonoscopy; diverticulitis or toxic megacolon; previous radiation therapy to the abdomen or pelvis; severe cardiovascular,  pulmonary, liver, or renal disease; and coagulation disorders or use of anticoagulants; incomplete colonoscopy or inadequate  bowel preparation. | | **Primary outcome of study:** accuracy of prediction ofsurveillance intervals, and NPV for adenomatous histology in the rectosigmoid colon  **Other relevant outcomes:** Diagnostic accuracy (sensitivity, specificity, PPV)  **Recruitment dates:** May 2011 to May 2012 | |
| **Participant characteristics** | | | | | | |
| **Age, years, mean (SD)** | 63 (10.4) | | | | | |
| **Other key patient characteristics (list)** | Male n=160 (58%); female n=118 (42%)  Clinical indication:  Screening n=102 (37%)  Surveillance n=76 (27%)  Symptoms n=100 (36%)  429/574 (75%) polyps were ≤5mm in size. 226/429 (53%) were  located in the rectosigmoid tract. | | | | | |
| **Endoscopist experience and training** | Five experienced endoscopists (1 at each center) performed all colonoscopies in the 5 selected centers. All had previous experience with high-definition, white-light endoscopy and NBI.  A library of endoscopic images and/or videos of NBI-classified hyperplastic and adenomatous polyps <10 mm was created for endoscopist training. All the collected images and/or videos corresponded to histologically verified polyps. An online training course on the differential characteristics between hyperplastic and adenomatous lesions was provided to all endoscopists. At the end of the training, each endoscopist was required to complete a qualifying examination in which an accuracy rate of 80% for differentiating between hyperplastic and adenomatous polyps <1 cm with NBI technology (20 cases) was required. If the operator accuracy was lower than the predefined threshold, the endoscopist had to repeat the  training course and the qualifying examination. | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Criteria are reported in the study publication (Table 1) but are not attributed to any named system. For each <10 mm polyp, the NBI criteria used to characterize the lesion were individually reported. Thereafter, each polyp was classified as type 1 (consistent with a hyperplastic polyp) or type 2 (consistent with an adenoma). It is stated (page 112) that most of the NBI individual criteria have been included in the NICE classification.  The Paris classification system was used to define polyp morphology. | | | | | |
| **Sample size calculation** | At an assumed threshold of 90% agreement for surveillance intervals, 280 patients were required to obtain a 3% precision of the estimates for the per-patient analysis. At an assumed NPV threshold of 90% for adenomatous histology of rectosigmoid diminutive lesions, 200 polyps were required, at an assumed 50% prevalence of adenomatous histology to obtain a 5% precision of the estimates for the per-polyp analysis. | | | | | |
| **Results** Polyps ≤ 5mm (n=429) | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | **Total** | |
| **Index test positive** | (a) 203\* | | | (b) 31\* | 234\* | |
| **Index test negative** | (c) 32\* | | | (d) 163\* | 195\* | |
| **Total** | 235 | | | 194 | 429 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 366\*/429 (85%) | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | |
| **Clinical sensitivity a / (a + c)** | | 86% | | | 82% - 90% | |
| **Clinical specificity d / (b + d)** | | 84% | | | 79% - 89% | |
| **PPV a / (a + b)** | | 87% | | | 82% - 91% | |
| **NPV d / (c + d)** | | 84% | | | 78% - 88% | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.41\* | | | 3.90 - 7.49\* | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.16\* | | | 0.12 - 0.22\* | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 33.4\* | | | 19.5 - 57.0\* | |
| Comments:  \* calculated by the reviewer as not reported in the publication. | | | | | | |
| **Results** Polyps ≤ 5mm predicted with high confidence (n=368) | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | (a) 175\* | | | (b) 21\* | | 196\* |
| **Index test negative** | (c) 20\* | | | (d) 152\* | | 172\* |
| **Total** | 195 | | | 173\* | | 368 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 327\*/368 (89%; 95% CI 86% - 92%) | | | | | |
| ***Diagnosis*** | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 90% | | | | 86%-94% |
| **Clinical specificity d / (b + d)** | | 88% | | | | 83%-93% |
| **PPV a / (a + b)** | | 89% | | | | 85%-94% |
| **NPV d / (c + d)** | | 89% | | | | 84%-93% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 7.39\* | | | | 4.94 to 11.07\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.12\* | | | | 0.08 to 0.18\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 63.3\* | | | | 33.1 – 121.3\* |
| Comments:  \* calculated by the reviewer as not reported in the publication. | | | | | | |
| **Results** Polyps ≤ 5mm in rectosigmoid region predicted with high confidence (n=204) | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | (a) 53\* | | | (b) 7\* | | 61\* |
| **Index test negative** | (c) 11\* | | | (d) 133\* | | 144\* |
| **Total** | 64 | | | 140\* | | 204 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 186\*/204 (91%; 95% CI 87% - 95%) | | | | | |
| ***Diagnosis*** | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 83% | | | | 74%-92% |
| **Clinical specificity d / (b + d)** | | 95% | | | | 91%-99% |
| **PPV a / (a + b)** | | 88% | | | | 80%-96% |
| **NPV d / (c + d)** | | 92% | | | | 88%-96% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 16.56\* | | | | 7.98 - 34.39\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.18\* | | | | 0.11 - 0.31\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 91.54\* | | | | 33.69 - 248.77\* |
| Comments:  \* calculated by the reviewer as not reported in the publication. | | | | | | |
| **Results** Polyps ≤ 5mm predicted with low confidence (n=61) | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | (a) 27\* | | | (b) 11\* | | 38\* |
| **Index test negative** | (c) 13\* | | | (d) 10\* | | 23\* |
| **Total** | 40 | | | 21\* | | 61 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 37\*/61 (61%; 95% CI 49%-73%) | | | | | |
| ***Diagnosis*** | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 68% | | | | 54%-82%\*\* |
| **Clinical specificity d / (b + d)** | | 48% | | | | 27%-69%\*\* |
| **PPV a / (a + b)** | | 71% | | | | 57%-86%\*\* |
| **NPV d / (c + d)** | | 43% | | | | 24%-64%\*\* |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 1.29\* | | | | 0.81 to 2.04\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.68\* | | | | 0.36 - 1.29\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 1.89\* | | | | 0.64 – 5.57\* |
| Comments:  \* calculated by the reviewer as not reported in the publication. | | | | | | |
| **Results** Polyps ≤ 5mm in rectosigmoid region predicted with low confidence (n=22) | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | (a) 5\* | | | (b) 5\* | | 10\* |
| **Index test negative** | (c) 7\* | | | (d) 5\* | | 12\* |
| **Total** | 12 | | | 10\* | | 22 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 10\*/22 (45%; 95% CI 25%-66%) | | | | | |
| ***Diagnosis*** | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | 42% | | | | 14%-70%\*\* |
| **Clinical specificity d / (b + d)** | | 50% | | | | 19%-81% |
| **PPV a / (a + b)** | | 50% | | | | 19%-81% |
| **NPV d / (c + d)** | | 42% | | | | 14%-70%\*\* |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 0.83\* | | | | 0.33 to 2.08\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 1.17\* | | | | 0.53 to 2.55\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 0.71\* | | | | 0.13 – 3.87\* |
| Comments:  \* calculated by the reviewer as not reported in the publication. | | | | | | |
| **Interpretability of test** | | Not reported | | | | |
| **Inter-observer agreement** | | Not reported | | | | |
| **Intra-observer agreement** | | Not reported | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | |
| **Adverse events** | | Not reported | | | | |
| **High confidence optical diagnosis** | | 368/429 polyps ≤5mm (86%) were predicted with high confidence. | | | | |
| **Low confidence optical diagnosis** | | 61/429 polyps ≤ (14%) were predicted with low confidence | | | | |
| **Number of polyps designated to be left in place** | | The discard strategy would have reduced by 48% the need for polypectomy. | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | |
| **Recommended surveillance interval** | | Of 278 patients there were 212 in whom a surveillance interval was able to be given, due to patients having *at least* 1 polyp ≤5mm characterised with high confidence (i.e. simulation of the resect and discard strategy). (NB. This is therefore a lower number of patients than the 280 required in the sample size calculation).  When a 5-year or 10-year interval for non-advanced adenomas ≤2 mm was given by using the U.S. guidelines, high confidence NBI characterization of polyps ≤ 5 mm predicted the correct surveillance interval in 92% of cases (95% CI 88%-96%) and 99% of cases (95% CI, 97%-100%), respectively, and in 99% of cases (95% CI, 97%-100%) according to the European guidelines. There were 17 patients with discrepancies between histopathology and NBI in prediction of surveillance intervals. According to the U.S. guidelines (when we admitted a 5-year interval for non-advanced adenomas ≤2 mm), the NBI-recommended surveillance would have been inappropriately anticipated for 5 of 278 patients (2%) and delayed in 12 of 178\* (4%) patients, whereas it would have been delayed in the 3 of  278 (1%) cases misclassified according to U.S. (with 10-year interval for ≤2 non-advanced adenomas) and European guidelines.  \* the publication states 178 but we presume it should be 278  The observed agreement rate between endoscopic and pathologic diagnosis appeared to be superior to the 90% threshold set by the ASGE (the PIVI criteria).  The resect and discard strategy would have reduced the need for post-polypectomy pathologic examination of the resected diminutive polyps by 86%.  *US guidelines*  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. Gastrointest Endosc 2011;73:  419-22.  Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps,  2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of  Radiology. Gastroenterology 2008;134:1570-95.  *European guidelines*  European guidelines for quality assurance in colorectal cancer screening and diagnosis. http://ec.europa.eu/health/major\_chronic\_diseases/  diseases/cancer/index\_en.htm#fragment3. | | | | |
| **Length of time to perform the colonoscopy** | | Not reported | | | | |
| **Number of outpatient appointments** | | Not reported | | | | |
| **Health related quality of life** | | Not reported | | | | |
| **Colorectal cancer** | | Not reported | | | | |
| **Mortality** | | Not reported | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients undergoing colonoscopy as part of screening, surveillance or investigation of symptoms | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The whole sample | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | All patients were diagnosed with histopathology | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Each polyp was resected and reviewed by a pathologist blinded to the optical diagnosis. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated, but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | A per patient analysis was performed for the estimation of surveillance intervals. The number of patients included in this analysis depended on whether or not a high confidence prediction had been made, plus the size of polyps detected. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes, no additional studies identified |

|  |
| --- |
| Summary reviewer’s comments |
| Results are based on the use of high definition NBI in a European (non-UK) population of patients undergoing colonoscopy as part of screening, surveillance or investigation of symptoms. Colonoscopy was performed by experienced endoscopists across 5 centres trained and qualified in the use of NBI. Predictions were made with high confidence, to inform surveillance intervals and decisions regarding whether to resect and discard diminutive polyps, and to leave hyperplastic polyps in the rectosigmoid area in situ (i.e. as per the PIVI statement). Surveillance intervals were predicted using US (ASGE) or European guidelines. |

**Rex et al.13**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | | | | **Participants** | | | **Outcome measures** | | | | |
| **Condition being diagnosed / detected:**  Determination of adenomatous versus hyperplastic or other non-adenomatous polyps.  **First author:** Rex  **Publication year:** 2009  **Country:** USA  **Study design:** Prospective cohort  **Number of centres:** 1  **Funding:** not reported  **Competing interests:** The author disclosed receiving research support and being a member of the speakers bureau for Olympus America Corporation. | **Index test:**  Narrow band imaging with the Olympus Exera 180 high-definition colonoscope. Identified polyps were assigned a designation of high or low confidence. A high confidence prediction was made if the polyp had one or more features associated with one histology (either adenomatous or hyperplastic) and no features associated with the other histology. A low confidence prediction was made when there was uncertainty about the features or if there were features of both adenomatous and hyperplastic polyps.  The 1.5x electronic magnification was not used if the prediction of polyp histology could be made with high-confidence without magnification.  **Reference standard:**  The attending pathologist’s report (histopathology) was accepted as the correct pathology. A subset of 30 polyps were reviewed by a specialist in gastrointestinal pathology who agreed with all the pathologists’ diagnoses. | | | | | | | **Number of participants:**  136 patients from whom 451 consecutively identified colorectal polyps were resected. The majority of the polyps n=395 were 5mm or smaller.  **Sample attrition/dropout:** not reported but none apparent so believed to be zero.  **Selection of participants:**  not reported  **Inclusion criteria for study entry:** not reported  **Exclusion criteria for study entry:** not reported | | | **Primary outcome of study:**  Accuracy of high-confidence endoscopic predictions of adenoma versus non-adenomatous histology for polyps 5mm or smaller in size.  **Other relevant outcomes:**  Surveillance intervals  **Recruitment dates:** not reported | | | | |
| **Participant characteristics** | | | | | | | | | | | | | | | |
| **Age, years, mean (SD)** | Not reported | | | | | | | | | | | | | | |
| **Other key patient characteristics (list)** | Total number of polyps = 451  Polyps 5mm or smaller n= 395  Polyps 6-9mm n= 33  Polyps 1cm or greater n= 23 | | | | | | | | | | | | | | |
| **Endoscopist experience and training** | A single endoscopist (the study author) who had a special interest in colonoscopy undertook the study. This endoscopist first created a library of 320 images which were used to determine polyp features consistently associated with adenomatous or hyperplastic histology. This could be considered to be the training received although it is not described as such. The endoscopist experience in colonoscopy in general or the Olympus Exera HD 180 colonoscope in particular is not described. | | | | | | | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Size and shape (Paris classification) were recorded for each polyp. In addition this study included an initial phase (not data extracted) in which a library of polyp photographs for 320 individual polyps photographed in both white and then blue light with the Olympus Exera HD 180 colonoscope was constructed. This library was used to determine which features were consistently associated with either adenomatous or hyperplastic polyps confirmed by histopathology. Five predictive features of adenoma are listed and three predictive features for hyperplastic polyps. The presence of these individual features was also recorded for each polyp. | | | | | | | | | | | | | | |
| **Sample size calculation** | Details for a sample size calculation are provided. In the study authors’ unit 80% of polyps removed were 5 mm or smaller, and approximately half of polyps 5 mm or smaller were adenomatous. It was estimated (based on a library of images from 320 polyps) that at least 80% of endoscopic determinations of polyp histology would be made with high confidence. The study author calculated that assuming accuracy of 93% for high-confidence interpretations, with a confidence interval of ±3%, a total of 278 polyps of 5mmor smaller would need to be examined prospectively with high confidence, or a total of 348 polyps 5 mm or smaller would need to be examined. The paper goes on to state that “To assess the association of accuracy with polyp size, we chose to estimate histology in consecutive polyps including those greater than 5 mm in size. Because 80% of resected polyps in our unit are 5 mm or smaller, a total sample size of 435 consecutive polyps was required for the prospective study, and a sample size of 450 consecutive colorectal polyps was chosen.” | | | | | | | | | | | | | | |
| **Results for all polyps 5mm or smaller in size** | | | | | | | | | | | | | | | |
|  | **Adenomatous polyps on histopathology** | | | | | | | **Hyperplastic or other non-adenomatous polyps on histopathology** | | | **Total** | | | | |
| **Index test positive** | 178 \* (a) | | | | | | | 28 \* (b) | | | 206 (a+b) | | | | |
| **Index test negative** | 17 \*(c) | | | | | | | 172 \* (d) | | | 189 (c+d) | | | | |
| **Total** | 195 (a+c) | | | | | | | 200 (b+d) | | | 395 (a+b+c+d) | | | | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 88.6% \* | | | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | **Value** | | | | | **95% CI** | | | | | |
| **Clinical sensitivity a / (a + c)** | | | | | 91.28% \* | | | | | 86.41% to 94.84% \* | | | | | |
| **Clinical specificity d / (b + d)** | | | | | 86.00 % \* | | | | | 80.41% to 90.49% \* | | | | | |
| **PPV a / (a + b)** | | | | | 86.41% \* | | | | | 80.96% to 90.77% \* | | | | | |
| **NPV d / (c + d)** | | | | | 91.01 % \* | | | | | 85.99% to 94.67% \* | | | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | 6.52 \* | | | | | 4.61 to 9.22 \* | | | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | 0.10 \* | | | | | 0.06 to 0.16 \* | | | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | 64.32 \* | | | | | 33.98 to 121.74 \* | | | | | |
| Comments: Endoscopic predictions of hyperplastic polyps were scored as being correct if the polyps were histopathologically hyperplastic or other non-adenomatous tissue.  \* - Calculated by the reviewer | | | | | | | | | | | | | | | |
| **Results for polyps 5mm or smaller in size with high-confidence predictions** | | | | | | | | | | | | | | | |
|  | | **Adenomatous polyps on histopathology** | | | | | | | **Hyperplastic or other non-adenomatous polyps on histopathology** | | | | | **Total** | |
| **Index test positive** | | 145 (a) | | | | | | | 15 \*(b) | | | | | 160 (a+b) | |
| **Index test negative** | | 7 \* (c) | | | | | | | 147 (d) | | | | | 154 (c+d) | |
| **Total** | | 152 \* (a+c) | | | | | | | 162 \* (b+d) | | | | | 314 \* (a+b+c+d) | |
| **Accuracy** ([a+d]/[a+b+c+d]) | | 93.0% \* | | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | | | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 95.39% \* | | | | | | 90.74% to 98.13% \* | | | |
| **Clinical specificity d / (b + d)** | | | | | | 90.74 % \* | | | | | | 85.19% to 94.72% \* | | | |
| **PPV a / (a + b)** | | | | | | 90.62% \* | | | | | | 85.01% to 94.66% \* | | | |
| **NPV d / (c + d)** | | | | | | 95.45 % \* | | | | | | 90.86% to 98.15% \* | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 10.30 \* | | | | | | 6.35 to 16.71 \* | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.05 \* | | | | | | 0.02 to 0.10 \* | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 203.0 \* | | | | | | 80.41 to 512.46 \* | | | |
| Comments: Endoscopic predictions of hyperplastic polyps were scored as being correct if the polyps were histopathologically hyperplastic or other non-adenomatous tissue.  For 6 (from a total of 15) polyps read with high confidence but called normal tissue after histopathology, the tissue blocks were recut and two showed adenoma in the recut tissue.  \* - Calculated by the reviewer | | | | | | | | | | | | | | | |
| **Results for polyps 5mm or smaller in size with low-confidence predictions** | | | | | | | | | | | | | | | |
|  | | | **Adenomatous polyps on histopathology** | | | | | | **Hyperplastic or other non-adenomatous polyps on histopathology** | | | | | | **Total** |
| **Index test positive** | | | 33 (a) | | | | | | 13 \*(b) | | | | | | 46 (a+b) |
| **Index test negative** | | | 10 \*(c) | | | | | | 25 (d) | | | | | | 35 (c+d) |
| **Total** | | | 43 \* (a+c) | | | | | | 38 \* (b+d) | | | | | | 81 \* (a+b+c+d) |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | 71.6% \* | | | | | | | | | | | | |
| ***Diagnosis*** | | | | | | | **Value** | | | | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | | 76.74% \* | | | | | | 61.37% to 88.24% \* | | |
| **Clinical specificity d / (b + d)** | | | | | | | 65.79 % \* | | | | | | 48.65% to 80.37% \* | | |
| **PPV a / (a + b)** | | | | | | | 71.74% \* | | | | | | 56.54% to 84.01% \* | | |
| **NPV d / (c + d)** | | | | | | | 71.43 % \* | | | | | | 53.70% to 85.36% \* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | | 2.24 \* | | | | | | 1.40 to 3.59 \* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | | 0.35 \* | | | | | | 0.20 to 0.64 \* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | | 6.346 \* | | | | | | 2.395 to 16.817 \* | | |
| Comments: Endoscopic predictions of hyperplastic polyps were scored as being correct if the polyps were histopathologically hyperplastic or other non-adenomatous tissue.  \* - Calculated by the reviewer | | | | | | | | | | | | | | | |
| **Interpretability of test** | | | | Not reported | | | | | | | | | | | |
| **Inter-observer agreement** | | | | Not applicable as only a single endoscopist | | | | | | | | | | | |
| **Intra-observer agreement** | | | | Not reported | | | | | | | | | | | |
| **Test acceptability (patients / clinicians)** | | | | Not reported | | | | | | | | | | | |
| **Adverse events** | | | | Not reported | | | | | | | | | | | |
| **High confidence optical diagnosis** | | | | For all polyps and for the polyps 5mm or smaller predicted to be adenomas, high-confidence predictions were more likely than low-confidence predictions to be accurate (p<0.001, chi-squared test). High confidence predictions of hyperplastic polyps were also more likely than low-confidence predictions to be accurate for all polyps and for polyps 5mm or smaller (p<0.001, chi-squared test) | | | | | | | | | | | |
| **All polyps** | | | | 368/451 (81.6%) \* predictions were made with high confidence  193/240 (80.4%) polyps predicted to be adenomas were predicted with high confidence  175/211 (82.9%) polyps predicted to be hyperplastic were predicted with high confidence | | | | | | | | | | | |
| **Polyps 5mm or smaller** | | | | 314/395 (79.5%) \* predictions were made with high confidence  160/206 \* (77.7%) polyps 5mm or smaller predicted to be adenomas were predicted with high confidence  154/189 (81.5%) polyps 5mm or smaller predicted to be hyperplastic were predicted with high confidence | | | | | | | | | | | |
| **Low confidence optical diagnosis - all polyps** | | | | 83/451 (18.4%) \* predictions were made with low confidence  47/240 (19.6%) \* polyps predicted to be adenomas were predicted with low confidence  36/211 (17.1%) \* polyps predicted to be hyperplastic were predicted low confidence | | | | | | | | | | | |
| **Polyps 5mm or smaller** | | | | 81/395 (20.5%) \* predictions were made with low confidence  46/206 \* (22.3%) \* polyps 5mm or smaller predicted to be adenomas were predicted with low confidence  35/189 (18.5%) \* polyps 5mm or smaller predicted to be hyperplastic were predicted with low confidence | | | | | | | | | | | |
| **Number of polyps designated to be left in place** | | | | Not reported | | | | | | | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | Not reported | | | | | | | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | Not reported | | | | | | | | | | | |
| **Recommended surveillance interval** | | | | The US Multi-Society Task Force-American Cancer Society guideline was used to guide recommended follow-up intervals. The pathology based recommendations used the pathologist’s report for each polyp. The endoscopic-based recommendations used the endoscopic prediction of histology for polyps of 5mm or smaller if it was a high-confidence prediction. If the polyp was 5mm or smaller but endoscopically predicted histology was made with low confidence or if the polyp was greater than 5 mm in size then the histopathological diagnosis was used. It was assumed that all polyps >5 mm in size would be sent for histopathology. | | | | | | | | | | | |
| **Assumption for recommended surveillance interval that clinical practice would be to perform colonscopy in 5 years for the finding of 1 or 2 tubular adenomas less than 1 cm in size.** | | | | For 128/136 (94%) of patients the recommendations for follow-up colonoscopy based on histopathology and endoscopic prediction were identical  For the eight patients where the recommendations differed between histopathology diagnosis and endoscopic prediction of polyps follow-up intervals, endoscopy-based recommendations were longer in 4 cases and shorter in 4 cases. | | | | | | | | | | | |
| **Assumption for recommended surveillance interval that clinical practice would be to perform colonscopy in 10 years for the finding of 1 or 2 tubular adenomas less than 1 cm in size.** | | | | For 134/136 (98.5%) of patients the recommendations for follow-up colonoscopy based on histopathology and endoscopic prediction were identical  For the three patients where the recommendations differed between histopathology diagnosis and endoscopic prediction of polyps follow-up intervals for endoscopy-based recommendations were longer in 1 case and shorter in 2 cases.  Reviewer note: there is a discrepancy in the paper which reports 134/136 recommendations as identical but identifies 3 patients where the recommendation differs. | | | | | | | | | | | |
| **Length of time to perform the colonoscopy** | | | | Not reported | | | | | | | | | | | |
| **Number of outpatient appointments** | | | | Not reported | | | | | | | | | | | |
| **Health related quality of life** | | | | Not reported | | | | | | | | | | | |
| **Colorectal cancer** | | | | Not reported | | | | | | | | | | | |
| **Mortality** | | | | Not reported | | | | | | | | | | | |
| \* - Calculated by the reviewer | | | | | | | | | | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Basic patient details (e.g. age, sex) are not reported. The reason(s) for patients having a colonoscopy are also not reported although the focus of the study appears to be on screening & surveillance. | Unclear |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The virtual chromoendoscopy assessment and polyp resection for histopathology occurred during the same colonoscopy. | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All resected polyps were assessed by histopathology | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Pathologists (number not stated) were blinded in all cases to the endoscopic prediction of histology. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The prediction of histopathology was made before the results of histopathology could be known. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | Not stated but believed to be zero. | No |
| 11 | Were withdrawals from the study explained? | Not explicitly stated but believed to be zero. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes - no additional references found |

|  |
| --- |
| Summary reviewer’s comments |
| A single endoscopist with a special interest in colonoscopy obtained these results from a patient population that was not described. It is therefore not clear which patients these results apply to and whether the same results could be obtained by other endoscopists. Furthermore the equipment used (Olympus Exera 180 high-definition colonoscope) was one of the first with high-definition and NBI capability but may since have been superseded by newer instruments with increased capabilities. |

**Rogart et al.75**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | **Participants** | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** WL with NBI for the differentiation of adenomatous from  non-adenomatous colorectal polyps during real-time colonoscopy  **First author:** Rogart et al  **Publication year:** 2008  **Country:** USA  **Study design:** Prospective study  **Number of centres:** 1(tertiary-referral centre at Yale University)  **Funding:** Not stated  **Competing interests: N**one declared. | **Index test:** White light (WL) with narrow-band imaging (NBI)  Olympus CF-H180AL colonoscopes (Olympus Corp, Center Valley, Pa) were used with Evis Exera II CV-180 processors (Olympus), with a xenon lamp as a light source and a colour charge-coupled device providing high-definition picture (1080 horizontal lines of resolution) when used with an HD monitor. Activation and deactivation of the double-band NBI filter (415 nm and 540 nm ±30 nm) is by pushing a button on the handle of the colonoscope.  The processor is also equipped with a x1.5 electronic magnification feature that can be activated with a separate button on the colonoscope and provides up to x70 total magnification.  The location, size, and shape of polyps were recoreded and images were electronically magnified to x1.5 the standard magnification. The endoscopist predicted the polyp type (adenoma, cancer or non-adenomatous) and level of confidence (low or high). Under the same magnification, NBI was activated, and the polyp was re-evaluated.  **Reference standard:**  Histopathology | | | | **Number of participants:** 131 (302 enrolled, of which 171 patients had no polyp)  **Sample attrition/dropout:**  **Selection of participants:** consecutive individuals  referred for routine colonoscopy to one of the study physicians  **Inclusion criteria for study entry:**   * only inclusion criteria was individuals referred for routine colonoscopy   **Exclusion criteria for study entry:**   * known or suspected familial polyposis syndromes * acute GI bleeding * international normalised ratio >2.0 or platelets <50,000/mm3 | | | **Primary outcome of study:** not stated  **Other relevant outcomes** (described as main outcomes): overall accuracy, sensitivity and specificity of endoscopic diagnosis by using WL alone and with NBI; improvement in endoscopists’ performance.  Also reported was inter-observer agreement of 20 test images (not data extracted).  **Recruitment dates:** August 2006 and July 2007 | |
| **Participant characteristics (n=131; 265 polyps)** | | | | | | | | | |
| **Age, years, mean (SD)** **(range):** 59 (10.0) (27 to 79) | | | | | | | | | |
| **Other key patient characteristics (list)** | | Male, n/N (%): 85/131 (65) | | | | | | | |
| Indication for colonoscopy, n (%) | | | | | | | |
| Screening: 72 (55) | | | | | | | |
| History of polyps: 24 (18) | | | | | | | |
| History of colorectal cancer: 8 (6) | | | | | | | |
| Heme and/or rectal blood: 14 (11) | | | | | | | |
| Anaemia: 5 (4) | | | | | | | |
| Other: 8 (6) | | | | | | | |
| **Endoscopist experience and training** | | 4 experienced endoscopists (≥1000 colonoscopies previously performed, range 1000-10,000), without extensive experience with NBI or chromoendoscopy.  Before the study began, the endoscopists attended a 1-hour interactive lecture on NBI. They were also given an ‘atlas’ showing endoscopic images of polyps examined with both chromoendoscopy and NBI. Laminated reference sheets with classifications, pictures and sketches were posted in each endoscopy room. Each endoscopist completed a pre-test on a separate day, consisting of 20 unknown polyps photographed with the NBI system and received fortnightly feedback about the accuracy of their endoscopic predictions compared with the histopathologic diagnosis throughout the study. After enrolment, the endoscopists completed a post-test involving the same 20 unknown polyps, which had been randomly re-ordered (mean score pre-test; mean score post-test 95%; p=0.55). | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | Simplified Kudo pit-pattern classification (reference provided in paper; stated that it ‘cannot yet be validated for NBI’ as it has been for chromoendoscopy) and vascular colour intensity (VCI) grading.  Endoscopists classified polyps as modified Kudo A (Kudo pit-pattern I or II, suggests non-adenomatous) or Kudo B (Kudo pit-patterns III-V, suggests adenomatous polyp or cancer) and then specified a specific pit-pattern (I-V). The VCI was graded by examining the mucosal hue of the polyp under NBI: light (same colour as surrounding mucosa), medium (mildly darker than surrounding mucosa, overall light-brown appearance), and dark (much darker than surrounding mucosa, dark brown or black in appearance). Image quality (good, fair, or poor) was  also recorded (not data extracted).  Polyp classification system for histopathological classification not explicitly reported but authors refer to 3 references when describing the adenomatous and serrated categories. | | | | | | | |
| **Sample size calculation** | | Not reported | | | | | | | |
| **Results** | | | | | | | | | |
| **NBI subgroup: 1 to 5 mm** | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | | **Total** |
| **Index test positive** | | | 71\* | | | Not reported | | | Not reported\*\* |
| **Index test negative** | | | 24\* | | | Not reported | | | Not reported\*\* |
| **Total** | | | (a+d) 95 | | | (b+d) 126 | | | (a+b+c+d) 265 |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | | | | Not reported | | | |
| ***Diagnosis*** | | | | | | **Value** | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 75% | Not reported | | |
| **Clinical specificity d / (b + d)** | | | | | | Not reported | Not reported | | |
| **PPV a / (a + b)** | | | | | | Not reported | Not reported | | |
| **NPV d / (c + d)** | | | | | | Not reported | Not reported | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | Not reported | Not reported | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | Not reported | Not reported | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | Not reported | Not reported | | |
| Comments: \* calculated by reviewer; \*\* not possible to calculate.  All endoscopists had approximately equal accuracy with NBI by the end of the study (improved by 13% from the 1st to the 2nd half of the study; p<0.05). However, also stated that 3 of the endoscopists showed significant improvements in diagnostic accuracies during the study, whereas one showed no change. | | | | | | | | | |
|  | | | | | | | | | |
| **Interpretability of test** | | | | Not reported | | | | | |
| **Inter-observer agreement** | | | | Inter-observer agreement was reported for 20 test images but not real-time assessment (not data extracted) | | | | | |
| **Intra-observer agreement** | | | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | | | Not reported | | | | | |
| **Adverse events** | | | | Not reported | | | | | |
| **High confidence optical diagnosis** | | | | Not reported for the 1 to 5 mm subgroup | | | | | |
| **Low confidence optical diagnosis** | | | | Not reported for the 1 to 5 mm subgroup | | | | | |
| **Number of polyps designated to be left in place** | | | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | Not reported | | | | | |
| **Recommended surveillance interval** | | | | Not reported | | | | | |
| **Length of time to perform the colonoscopy** | | | | Not reported | | | | | |
| **Number of outpatient appointments** | | | | Not reported | | | | | |
| **Health related quality of life** | | | | Not reported | | | | | |
| **Colorectal cancer** | | | | Not reported | | | | | |
| **Mortality** | | | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Majority of patients were undergoing colonoscopy for screening, surveillance (history of polyps) or due to having symptoms suggestive of colorectal cancer. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All polys found were histopathologically assessed. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | 2 pathologists (with either expertise or special interest in GI pathology) were blinded to the endoscopic images and predictions. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | No withdrawal apparent | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant publications were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| The population sample was based on patients from the USA undergoing routine colonoscopy and it is unclear how representative this sample is of the patient population in the UK age range 27 to 79 years), and how similar endoscopists training is compared to training received in the NHS. Study was performed in a single academic centre, so the results may not be applicable to a wider range of settings. |

**Shahid et al.76**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | | **Participants** | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Comparison of probe-based confocal laser endomicroscopy (pCLE) and narrow band imagining (NBI) for predicating histology of small colorectal polyps (<10 mm), including combining both methods against histopathology.  **First author:** Shahid et al.  **Publication year:** 2012  **Country:** USA  **Study design:** Prospective cohort  **Number of centres:** 1 (tertiary referral hospital)  **Funding:** None reported. One of the authors receives research grant support from Mauna Kea Technologies, Olympus and Fujinon Corporations.  **Competing interests:** Stated none, but see funding above. | **Index test:**  High-definition colonoscope (CFH180 or PCF H 180, Olympus, Center Valley, NY), processor (CV 180 Excera, Olympus), high-definition monitor and 4-mm clear cap distal attachment Olympus D-201-15004).  pCLE details not data extracted, as not real-time.    Polyps were first screened by white-light, high-definition colonoscopy. At first polyp (either during advancement or withdrawal, before or after cecal intubation) the mucus was washed away and the NBI mode was used to make a diagnosis, with the endoscopist blinded to pCLE imaging.  **Reference standard:** Histopathology | | | | **Number of participants:** 65  **Sample attrition/dropout:**  no dropouts reported  **Selection of participants:** Consecutive patients were recruited in a tertiary referral centre.  **Inclusion criteria for study entry:** age ≥18 years, with polyps <10 mm during surveillance or screening colonoscopies.  **Exclusion criteria for study entry:** non-corrected coagulopathy, pregnancy, breast feeding, documented allergy to fluorescein, patients with no colorectal lesions found during a study colonoscopy, and any patient previously reported on by the authors. | | **Primary outcome of study:** not stated  **Other relevant outcomes:** sensitivity, specificity, accuracy, PPV, NPV, and positive and negative likelihood ratios of pCLE and NBI for predicting histology (neoplastic vs non-neoplastic)  **Recruitment dates:** April 2008 to April 2010 | |
| **Participant characteristics** | | | | | | | | |
| **Age, years, median (range)** | | 69 (44-91) | | | | | | |
| **Other key patient characteristics (list)** | | Male, n/N (%): 40/65 (62) | | | | | | |
| Caucasians, n (%): 64 (98.5) | | | | | | |
| Number of colorectal lesions: 130 | | | | | | |
| Number of polyps, n (%): | | | | | | |
| 1: 31 (48) | | | | | | |
| 2: 15 (23) | | | | | | |
| 3: 11 (17) | | | | | | |
| 4: 6 (9) | | | | | | |
| 6: 2 (3) | | | | | | |
| 103 polyps were sized 1-5 mm. Of these, 45 were neoplastic and 58 were non-neoplastic. | | | | | | |
| **Endoscopist experience and training** | | One endoscopist, who was an expert in advanced imaging methods and had performed ≥100 pCLE procedures, conducted all examinations. Unclear how experienced the endoscopist was with NBI. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | Surface pit pattern of the lesion was classified according to Kudo criteria as modified by San *et al.* for NBI (criteria were developed using magnification endoscopes, not used in this study). Round and stellate pit and vascular patterns represented benign, hyperplastic lesion, and villiform, gyrus-like irregular patterns represented neoplastic lesions. The anatomical site and morphological class of legions was recorded during the procedure according to the Paris classification.  Intraepithelial neoplasia was assessed by the pathologist using modified Vienna criteria. | | | | | | |
| **Sample size calculation** | | Not reported. Stated that a limitation of the study was” a relatively small sample size and corresponding lack of power to detect smaller differences in the accuracy, sensitivity and specificity of identifying neoplastic lesions between methods. A larger sample is necessary to estimate diagnostic measures with higher precision and also to rule out other potentially meaningful differences that were not found to be statistically significant” in the study. | | | | | | |
| **Results** | | | | | | | | |
| **NBI subgroup (1-5 mm)** | | | **Adenomatous polyps on histopathology1** | | | **Hyperplastic polyps on histopathology2** | | **Total** |
| **Index test positive** | | | (a) 27 | | | (b) 3\* | | 30 |
| **Index test negative** | | | (c) 18\* | | | (d) 55 | | 73 |
| **Total** | | | 45 | | | 58 | | 103 |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | 80% (95% CI, 70% to 87%) | | | | | |
| ***Diagnosis*** | | | | **Value** | | | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | 60% | | | | 45% to 73% |
| **Clinical specificity d / (b + d)** | | | | 95% | | | | 85% to 98% |
| **PPV a / (a + b)** | | | | 90% | | | | 72% to 96% |
| **NPV d / (c + d)** | | | | 75% | | | | 62% to 84% |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | 11.60 | | | | 3.76 to 35.82\* |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | 0.42 | | | | 0.29 to 0.61\* |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | 27.500\* | | | | 7.449 to 101.528\* |
| Comments: \* calculated by reviewer. CIs differ to values calculated by reviewer. Data for pCLE subgroup (1-5 mm) not extracted.  1 defined as neoplastic; 2 defined as non-plastic. | | | | | | | | |
| **Interpretability of test** | | | | Not reported | | | | |
| **Inter-observer agreement** | | | | Not reported | | | | |
| **Intra-observer agreement** | | | | Not reported | | | | |
| **Test acceptability (patients / clinicians)** | | | | Not reported | | | | |
| **Adverse events** | | | | Stated that none of the patients experienced any endoscopic complications. Most patients had transient yellow discoloration of the skin and urine, resolved within 1 to 2 hours for skin and 24 hours for urine. | | | | |
| **High confidence optical diagnosis** | | | | Not reported | | | | |
| **Low confidence optical diagnosis** | | | | Not reported | | | | |
| **Number of polyps designated to be left in place** | | | | Not reported | | | | |
| **Number of polyps designated to be resected and discarded** | | | | Not reported | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | Not reported | | | | |
| **Recommended surveillance interval** | | | | Not reported | | | | |
| **Length of time to perform the colonoscopy** | | | | Not specifically stated. NBI inspection time was typically <1 minute. The average withdrawal time during most colposcopy procedures at the centre was 8 to 10 minutes (generally, not specifically in this study), making a procedure more than 11 minutes at a minimum. | | | | |
| **Number of outpatient appointments** | | | | Not reported | | | | |
| **Health related quality of life** | | | | Not reported | | | | |
| **Colorectal cancer** | | | | Not reported | | | | |
| **Mortality** | | | | Not reported | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Patients were referred for screening and surveillance colonoscopies | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The whole sample received verification using the intended reference standard. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Stated that all tissue specimens were examined by a gastrointestinal pathologist, blinded to the pCLE information. Presumed that this also applied to the results of the NBI. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | Stated that per routine practice, only the site and anatomic location was provided. | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | While not specifically stated, there appear to have been no withdrawals. | Yes |

yes / no / unclear;

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant publications were identified. |

|  |
| --- |
| Summary reviewer’s comments |
| Patients were American with an age range of 44-91 years, recruited in a tertiary referral hospital. It is unclear how representative this USA population is compared to a UK population, considering the age (median age 69 years) and ethnicity (98.5% Caucasian) of those included in the study. Included patients were undergoing screening and surveillance colonoscopies, but exact indication for colonoscopy were not provided. Therefore, it is unclear how relevant the patient population in this study is to the population of interest in this appraisal. |

**Sola-Vera et al.14**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | | **Participants** | | | | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Accuracyof optical diagnosis of diminutive colon polyps and of (secondary aims) <10 mm polyps, and usefulness of optical diagnosis as a tool for predicting future colonoscopy surveillance interval**.**  **First author:** Sola-Vera et al  **Publication year:** 2015  **Country:** Spain  **Study design:** Prospective cohort study  **Number of centres:** 1(endoscopic unit in medium size academic public hospital with 450 beds)  **Funding:** None  **Competing interests:** First author was collaborating with Olympus Iberia in training courses on optical diagnosis. | **Index test:** NBI. Exera II (Olympus Medical System, Tokyo, Japan) processor and high definition monitors in three examination rooms; one room equipped with a processor not suitable for optical diagnosis (no high definition processor). CF-H180AL (high definition) and CF-Q180AL (high resolution) Olympus colonoscopies were used (no statistical significant differences in results between endoscopes, p=0.4).  One photo with NBI and another with white light were taken of all the polyps. Endoscopists scored the polyps and registered the confidence level and if possible, recommended a surveillance interval at the end of the procedure, and for each polyp recorded the location, estimated the size (compared to open biopsy forceps or snare sheath) and the morphology (Paris classification). Polyp characteristics were evaluated in real-time (i.e. not by using photos).  **Reference standard:**  Histopathology | | | **Number of participants:** 195 (822 patients submitted for colonoscopy, reasons for exclusion of 627 patients provided; 90/ 195 patients included for surveillance intervals, reasons for exclusions only provided for 101 patients)  **Sample attrition/dropout:** none reported  **Selection of participants:** consecutive adults patients referred for colonoscopy  **Inclusion criteria for study entry:** patients aged >18 years  **Exclusion criteria for study entry:**   * Patients examined in the room containing the equipment not suitable for optical diagnosis * Rectosigmoidoscopy was requested * Patients without polyps * Patients with an obvious colon cancer without simultaneous polyps   Exclusion criteria for the purposes of predicting  future colonoscopy surveillance intervals were:   * Preparation of the colon not adequate (poor or inadequate, Aronchick scale) * Incomplete colonoscopy, hereditary polyposis syndromes * Personal history of inflammatory bowel disease, * Obvious colorectal cancer detected without polyps * Some polyps not resected and/or not recovered. | | | | | | **Primary outcome of study (described as main outcomes):** sensitivity, specificity, negative and positive predictive value, likelihood ratios and diagnostic odds ratio of diminutive and small adenomatous polyps, all predictions and those made with high confidence.  **Other relevant outcomes (described as secondary outcomes):**  Accuracy of optical diagnosis as a function of size and location of polyps, dedication of endoscopists and type of endoscope (not data extracted). The correlation between optical diagnosis and pathological diagnosis when recommending a follow-up interval after colonoscopy.  **Recruitment dates:** November 2013 and January 2014 | |
| **Participant characteristics (total sample)** | | | | | | | | | | | |
| **Age, years, mean (SD)** | | 64.0 (12.4) | | | | | | | | | |
| **Other key patient characteristics (list)** | | Male, %: 55.9 | | | | | | | | | |
| Reason for colposcopy, n (%) | | | | | | | | | |
| Colorectal cancer screening: 42 (21.5) | | | | | | | | | |
| Positive faecal occult blood test: 32 (16.4) | | | | | | | | | |
| Rectal bleeding: 33 (16.9) | | | | | | | | | |
| Polyps/colorectal cancer surveillance 31 (15.9) | | | | | | | | | |
| Anaemia: 16 (8.2) | | | | | | | | | |
| Other: 41 (21.1) | | | | | | | | | |
| Diminutive (≤ 5 mm) polyps, n/N (%):  219/401 (54.6) – 3 could not be recovered, final sample n=216 | | | | | | | | | |
| **Endoscopist experience and training** | | 5 expert endoscopists were divided into 2 categories according to their dedication to endoscopy (2 full-time and 3 part-time, i.e. <30% of annual working time). All had completed >5000 colonoscopies, but only 1 had experience in the characterisation of colon polyps with NBI. All endoscopists received training on the characterisation of colon polyps with NBI using the NICE classification on still images (a pre-test, a learning phase and a post-test) and all achieved 90% accuracy for optical diagnosis in the post-test. It was recommended that all parameters taken during the procedure were dictated to a nurse in real time.  During the study endoscopists were encouraged to compare the pathological diagnosis with their optical diagnosis prediction, in a continuous process of self-learning. | | | | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | NICE classification (Type 1. Hyperplastic polyp, Type 2. Adenomatous polyp, Type 3. Cancer with deep submucosal invasion). Paper stated that for purposes of analysis, all sessile serrated and traditional adenomas were considered as non-adenomatous in this study, since the NCIE classification includes them in the same category as hyperplastic polyps.  During endoscopy polyp size, location and the morphology were determined according Paris classification.  Pathologist followed the WHO classification for digestive tumours and the histopathological diagnosis was standardised in all cases. | | | | | | | | | |
| **Sample size calculation** | | Stated that 239 polyps <10 mm were needed, assuming a sensitivity of optical diagnosis of 91%. Assuming that 80% of the predictions would be made with high confidence, the total number of polyps <10 mm needed was 299. This figure as increased by 5% to compensate for possible losses – 315 polyps <10 mm were identified but 4 could not be recovered, leaving at total of 311. | | | | | | | | | |
| **Results** | | | | | | | | | | | |
| **All predictions for the subgroup diminutive polys (n=216)** | | | | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | | | | | | (a) 85 | | | (b) 8\* | | 93\* |
| **Index test negative** | | | | | | (c) 70\* | | | (d) 53 | | 123\* |
| **Total** | | | | | | 155 | | | 61 | | 216 |
| Accuracy ([a+d]/[a+b+c+d]) | | | | | | 63.9% (138/216) | | | | | |
| ***Diagnosis*** | | | | | | **Value** | | | 95% CI | | |
| **Clinical sensitivity a / (a + c)** | | | | | | 55% | | | 47% to 63% | | |
| **Clinical specificity d / (b + d)** | | | | | | 87 % | | | 78% to 96% | | |
| **PPV a / (a + b)** | | | | | | 91% | | | 85% to 98% | | |
| **NPV d / (c + d)** | | | | | | 43% | | | 34% to 52% | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | 4.18 | | | 2.16 to 8.1 | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | 0.52 | | | 0.43 to 0.63 | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | 8.04 | | | 3.59 to 18.05\* | | |
| Comments: *\** calculated by reviewer. | | | | | | | | | | | |
| **High confidence predictions for the subgroup diminutive polys (n=166)** | | | | | | **Adenomatous polyps on histopathology** | | | **Hyperplastic polyps on histopathology** | | **Total** |
| **Index test positive** | | | | | | 67 | | | 4\* | | 71\* |
| **Index test negative** | | | | | | 47\* | | | 44 | | 91\* |
| **Total** | | | | | | 114 | | | 48 | | 162 |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | 68.5% (111/162) | | | | | | | | |
| ***Diagnosis*** | | | | | | | **Value** | **95% CI\*\*** | | | |
| **Clinical sensitivity a / (a + c)** | | | | | | | 59% | 50% to 69% | | | |
| **Clinical specificity d / (b + d)** | | | | | | | 92% | 83% to 100% | | | |
| **PPV a / (a + b)** | | | | | | | 95% | 89% to 100% | | | |
| **NPV d / (c + d)** | | | | | | | 48% | 37% to 59% | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | | 7.12 | 2.75% to 18.41% | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | | 0.44 | 0.35% to 0.56% | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | | 16.2 | 5.275 to 46.61\* | | | |
| Comments: \* calculated by reviewer; \*\* the reviewer believes that must be an error in the paper because the paper states 166/216 of the prediction s for diminutive polyps were high confidence and then that optical diagnosis adequately predicted 67/114 adenomas and 44/48 hyperplasic. With the values shown above in the 2x2 table slightly different 95% CIs are obtained for sensitively and specificity, and the PPV, +VR LR and –VR LR and DOR are slightly different (94%, 7.05, 0.45 and 15.68; respectively). | | | | | | | | | | | |
|  | | | | | | | | | | | |
| **Interpretability of test** | | | | | Not reported | | | | | | |
| **Inter-observer agreement** | | | | | Not reported | | | | | | |
| **Intra-observer agreement** | | | | | Not reported | | | | | | |
| **Test acceptability (patients / clinicians)** | | | | | Not reported | | | | | | |
| **Adverse events** | | | | | Not reported | | | | | | |
| **High confidence optical diagnosis** | | | | | High confidence diagnosis if the polyps had ≥1 characteristic of one type and none of the other. 166/216 (76.9%) of the prediction of the histology of the diminutive polyps were made with high confidence. | | | | | | |
| **Low confidence optical diagnosis** | | | | | While not specifically stated it can be deducted that 50/216 (23.1%) of the prediction of the histology of the diminutive polyps were made with low confidence. | | | | | | |
| **Number of polyps designated to be left in place** | | | | | Not reported | | | | | | |
| **Number of polyps designated to be resected and discarded** | | | | | Not reported | | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | | Not reported | | | | | | |
| **Recommended surveillance interval** | | | | | Surveillance intervals were based on histopathology and optical diagnosis using the European and ESGE guidelines and could only be made for 90/195 patients (i.e. 46% - % calculated by reviewer). Agreement of histopathology and optical diagnosis for diminutive polyps based on a possible 47 cases were the same for follow-up for 46/47 (97.8%) for both guidelines (European guidelines106 and ESGE guidelines107). Surveillance intervals are only provided for the total sample (n=90) (not data extracted) and not reported separately for patients with diminutive polyps. | | | | | | |
| **Length of time to perform the colonoscopy** | | | | | Not reported | | | | | | |
| **Number of outpatient appointments** | | | | | Not reported | | | | | | |
| **Health related quality of life** | | | | | Not reported | | | | | | |
| **Colorectal cancer** | | | | | Not reported | | | | | | |
| **Mortality** | | | | | Not reported | | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Majority of patients referred for screening, surveillance colonoscopy or colonoscopy to investigate symptoms suggestive of colorectal cancer. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | The whole sample received verification using the intended reference standard. | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Stated that pathologist did not know the endoscopist prediction for each polyp. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | Endoscopists would not have known the histopathology results for the polyp when they made their prediction. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? | Polyps were sent in a separate for histopathological analysis. | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | While not specifically stated, there appear to have been no withdrawals. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant reverences were identified. |

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| Summary reviewer’s comments |
| The population sample was based on patients from Spain and it is unclear how representative the population is of the patient population in the UK, and how similar endoscopists training is compared to training received in the NHS. Only one of the five endoscopists in this study had experience in using NBI. Study was performed in a single centre, so the results may not be applicable to a wider range of settings. Patients were scheduled to undergo colonoscopy, but in over 20% of patients exact indication for colonoscopy was not provided. Around 80% of patients in the study had indication relevant to the appraisal. |

**Vu et al.77**

|  |  |  |  |  |  |  |  |  |
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| **Reference and design** | **Diagnostic tests** | | | **Participants** | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Comparison of surveillance interval recommendations and diagnostic performance between ‘resect and discard’ and standard of care (histopathology) of diminutive polyps  **First author:** Vu et al.  **Publication year:** 2015  **Country:** USA  **Study design:** Prospective cohort  **Number of centres:** 1 (hospital outpatient endoscopy centre)  **Funding:** Nonereported  **Competing interests:** none for 7 authors.  GSS: grant (K23 DK84113);  SAE: consultant and medical advisory board, Olympus corporation); | **Index test:** High-definition white light (HDWL) or narrow-band imaging (NBI - at the discretion of the endoscopist).  Real-time imaging using HDWL or NBI (polyps are resected and discarded rather than being sent for pathological review).  The colonoscopes used were Olympus CF-H180 AL with HDWL and NBI capability in conjunction with  the Evis Evera II CV-180 video processor and OEV 191H 19-inch high-definition monitor (Olympus America Inc, Center Valley, PA).  **Reference standard:**  Histopathology  \* It is unclear if the 64% refers to the 95.7% overall histological prediction made for diminutive polyps or the 74.2% made with high confidence | | | **Number of participants:** 315 (618 patients underwent colonscopy, 303 excluded: 262 without diminutive polyps, 35 with poor bowl preparation and 6 with no histopathological diagnosis)  **Sample attrition/dropout:** none reported  **Selection of participants:** Consecutive patients undergoing colonoscopy for colorectal cancer (CRC) screening or surveillance indications  **Inclusion criteria for study entry:**   * adults (no age criteria stated) * identified with diminutive polyps (defined as ≤5 mm) at colonoscopy   **Exclusion criteria for study entry:**   * colonoscopy was performed for an indication other than screening or surveillance * no diminutive polyps were found * an optical or histopathological diagnosis of the diminutive polyp could not be made * the polyp was resected but not retrieved for histopathology * a synchronous CRC was identified at the time of the colonoscopy * post hoc diagnoses of polyposis syndromes and inflammatory bowel disease were made * colonoscopy was not complete to cecum * fair or poor bowel preparation (defined as a Boston bowel preparation scale (BBPS) score) | | | **Primary outcome of study:** concordance of recommended surveillance intervals  (1. endoscopist’ prediction of diminutive polyps by optical diagnosis using HDWL and/or NBI) and 2. final histopathological diagnosis)  **Other relevant outcomes:** accuracy, sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of histology predictions by optical diagnosis using HDWL with/without  NBI.  Subgroup analyses: diagnostic performance  by level of confidence in prediction, type of endoscopist  (academic vs. community), and use of NBI (not data extracted)  **Recruitment dates:** October 2011 and October 2012 | |
| **Participant characteristics (n=315; 606 diminutive polyps)** | | | | | | | | |
| **Age, years, mean (SD):** 62.4 (8.7) | | | | | | | | |
| **Other key patient characteristics (list)** | | Male, n/N (%): 161/315 (51) (n calculated by reviewer) | | | | | | |
| Indication, n (%) | | | | | | |
| Screening: 152 (48.3) | | | | | | |
| First colonoscopy: 83 (26.7 – calculated by reviewer as 26.3%) | | | | | | |
| Surveillance: 163 (51.7) | | | | | | |
| Personal history of colorectal cancer: 6 (1.9) | | | | | | |
| Mean size polyp, mm (SD): 3.64 (1.04) | | | | | | |
| Polyp location (%) | | | | | | |
| Proximal colon: 53 | | | | | | |
| Distal colon: 47 | | | | | | |
| **Endoscopist experience and training** | | 4 academic and 2 community gastroenterologists. All were highly experienced and had performed >5,000 colonoscopies each.  Endoscopists formally reviewed images of surface patterns of adenomatous and non-adenomatous polyps in HDWL and NBI using a validated study image set prior to the study (reference provided in paper) at study onset, as well as attending a formal structured teaching session led by the senior author (DSE) to review the polyp surface mucosal and vascular patterns and pit patterns of adenomatous and non-adenomatous lesions. HDWL and NBI images of multiple polyps were then reviewed and discussed in detail until all endoscopists were confident in their recognition. The image set was also available to endoscopists at all times including in each procedure room for self-review throughout the study. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | | None stated. All resected polyps were processed in standard fashion. Polyps were classified into adenoma or non-adenomatous polyp, which included hyperplastic polyps, inflammatory polyps, or normal mucosa. For purposes of analysis, sessile serrated adenomas/polyps were grouped with adenomas given that surveillance recommendations for these lesions are similar to that of adenomas. | | | | | | |
| **Sample size calculation** | | Stated that testing the null hypothesis that the proportion positive was identical in the two populations, a proposed sample size of 300 patients was determined for the study to have power of 89.7 % to yield a statistically significant result when the criterion for significance was set at alpha of 0.05 and a two-tailed testing was applied. | | | | | | |
| **Results** | | | | | | | | |
| **NBI** | | | **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 | | 388 |
| **Accuracy** ([a+d]/[a+b+c+d]) | | | | | | 73.9% | | |
| ***Diagnosis*** | | | | | | **Value** | | **95% CI** |
| **Clinical sensitivity a / (a + c)** | | | | | | Not reported | | Not reported |
| **Clinical specificity d / (b + d)** | | | | | | Not reported | | Not reported |
| **PPV a / (a + b)** | | | | | | Not reported | | Not reported |
| **NPV d / (c + d)** | | | | | | Not reported | | Not reported |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | | | | | Not reported | | Not reported |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | | | | | Not reported | | Not reported |
| **Diagnostic odds ratio (a x d)/(b x c)** | | | | | | Not reported | | Not reported |
| Comments: Histological prediction could be made for 580/606 (95.7 %) of diminutive polyps, with high confidence in 74.2 %. NBI was used in 64 % of these predictions, but it is unclear if this refers to overall histological prediction made for diminutive polyps or those made with high confidence.  NBI failed to improve prediction accuracy in high prediction confidence cases (78.6 %) and in low prediction confidence cases (60.8 %).  Variability in the use of NBI ranged from 3.4% to 88.4 %, with lower NBI use among community compared to academic endoscopists (13.2% vs. 75.8 % of cases, p<0.001). | | | | | | | | |
| **Interpretability of test** | | | | | Not reported | | | |
| **Inter-observer agreement** | | | | | Not reported | | | |
| **Intra-observer agreement** | | | | | Not reported | | | |
| **Test acceptability (patients / clinicians)** | | | | | Not reported | | | |
| **Adverse events** | | | | | Not reported | | | |
| **High confidence optical diagnosis** | | | | | High confidence accuracy was calculated using high-confidence predictions defined as visual analogue scale score ≥7.  High confidence accuracy with NBI: 78.6%. | | | |
| **Low confidence optical diagnosis** | | | | | Low confidence accuracy with NBI: 60.8%. | | | |
| **Number of polyps designated to be left in place** | | | | | Not reported | | | |
| **Number of polyps designated to be resected and discarded** | | | | | Not reported | | | |
| **Number of polyps designated for resection and histopathological examination** | | | | | Not reported | | | |
| **Recommended surveillance interval** | | | | | Surveillance intervals (based on the US Multi-Society Task Force guidelines for colorectal surveillance 101, 102) for patients with:   * no polyps or small (<10 mm) hyperplastic polyps: 10 years * 1–2 small tubular adenomas: 5 years * 3–10 tubular adenomas: 3 years * ≥10 adenomas: 1 year * adenoma ≥10 mm in size, with villous features, or high-grade dysplasia: 3 years   Confidence in NBI prediction (mean visual analogue scale score): 7.6 (SD 3.2).  Concordance in surveillance interval recommendations: 84.1% with NBI (calculated using high-confidence predictions defined as visual analogue scale ≥7). | | | |
| **Length of time to perform the colonoscopy** | | | | | Not reported | | | |
| **Number of outpatient appointments** | | | | | Not reported | | | |
| **Health related quality of life** | | | | | Not reported | | | |
| **Colorectal cancer** | | | | | Not reported | | | |
| **Mortality** | | | | | Not reported | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

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| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Adult outpatients undergoing colonoscopy for colorectal cancer screening or surveillance indications. | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard. | Yes |
| 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? |  | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | All resected polyps were processed in standard fashion and interpreted by histopathologists | Yes |
| 5 | Did patients receive the same reference standard irrespective of the index test result? |  | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | Histopathologists were blinded to the polyp predictions. | Yes |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? |  | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? |  | No |
| 11 | Were withdrawals from the study explained? | While not specifically stated, there appear to have been no withdrawals. | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes. No additional relevant publications were identified. |

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| Summary reviewer’s comments |
| The population sample was based on patients from the USA, who were undergoing colonoscopy for routine clinical indications (surveillance and screening). Endoscopists were a mixture of academic and community gastroenterologists and it is unclear how similar their training is compared to training received in the NHS. Study was performed in a single centre, so the results may not be applicable to a wider range of settings. |

**Wallace et al.12**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference and design** | **Diagnostic tests** | | **Participants** | | | **Outcome measures** | |
| **Condition being diagnosed / detected:** Differentiation of neoplastic from non-neoplastic polyps. Aim of study was to compare dual-focus colonoscopy with standard colonoscopy with respect to the ASGE guidelines.  **First author:**  Wallace et al.  **Publication year:** 2014  **Country:** USA  **Study design:** RCT, with one arm relevant to our review.  **Number of centres:** 1 (an academic medical centre ambulatory surgical centre)  **Funding:** Olympus Corporation of America.  **Competing interests:**  One of the authors (MW) has received research funding from Olympus, BSCI, Fujinon, Ninepoint Medical Rieger-Johnson, and Exact Sciences. CA has received grants from Olympus Inc. AK received grants from GlaxoSmithKline and Gilead Sciences. JC received funding from Boston Scientific, Olympus, GI Supply, and Masimo Corporation. EB received funding from Rhythm Pharmaceuticals Inc. Another from Abbott Laboratories. The final author received grants from Pfizer (MP). | **Index test:**  High definition (HD) white-light imaging (WLI) and narrow-band imaging (NBI). Olympus CF-H180 and Exera II 180 colonoscopes, Olympus.  HD WLI and NBI dual-focus colonoscopy (Olympus CF-HQ190 and Exera III 190 colonoscopes, Olympus) was used in the other study arm, but data have not been extracted from this arm as near focus (i.e. magnification) was used.  **Reference standard:**  Histopathology. | | **Number of participants:**  264 study completers in the 180 arm (296 were randomised to this arm). Number of participants in the diminutive polyps subgroup analyses not reported.  Overall in the study, 600 patients were enrolled and 593 were randomised.  **Sample attrition/dropout:**  32 (11%\*) patients in the 180 arm were excluded after randomisation. (% calculated by reviewer).  The most common reasons for exclusion post-randomisation in the total sample (n): scheduling difficulties (16), and lack of pediatric 190 colonoscope with anatomic issues (25). Breakdown of reasons not provided for each arm separately.  **Selection of participants:**  Patients at ‘average risk’ undergoing colonoscopy were considered for the study.  **Inclusion criteria for study entry:**  As above.  **Exclusion criteria for study entry:**  Acute bleeding or active colitis; family or a personal history of polyposis syndrome; history of inflammatory bowel disease; previous bowel surgery; inadequate bowel preparation. | | | **Primary outcome of study:**  Accuracy (neo-plastic versus non-neoplastic)  **Other relevant outcomes:**  Diagnostic sensitivity, specificity, NPV, PPV and surveillance intervals. Study also provides data on procedure times, confidence levels and subgroup analyses of ≤5mm and rectosigmoid diminutive polyps.  **Recruitment dates:**  Not reported. | |
| **Participant characteristics** | | | | | | | |
| **Age, years, median (minimum, 25th percentile, 75th percentile, maximum)** | 60 (33, 55, 70, 85) | | | | | | |
| **Other key patient characteristics (list)** | 375 patients had at least one polyp identified, but of these patients, 3 had no histopathology = 372 patients in the overall final sample for analysis.  In total, 927 polyps (from 372 patients) were analysed, although Table 4 states 963 polyps were characterised. Of the 488 polyps characterised, 321 (66%) diminutive polyps (≤ 5mm) were characterised in the NBI 180 arm. Of these, 310 were included in the statistical analyses of diminutive polyps data. Data in Table 5 (p. 1078) shows 10 diminutive polyps not assessed by histopathology, and footnote to Table 6 (p. 1079) shows one patient missing predicted pathology for WLI only (states polyp removed from analysis).  Polyp shape: of the 321 identified diminutive polyps, 265 (83%) were sessile, 54 (17) flat and 3 other (<1%). Histopathology: 159 (50%) were non-neoplastic and 152 (47%) were neoplastic.  Gender, female, n (%): 112 (42%) (180 NBI arm, all polyps).  Reasons for this colonoscopy, n (%): routine 122 (46%), surveillance 114 (43%), diagnosis 27 (10%), and other 1 (<1%) (180 NBI arm, all polyps). | | | | | | |
| **Endoscopist experience and training** | Seven endoscopists performed the colonoscopies. All of the study endoscopists underwent training on a simplified NBI International Classification for Endoscopy before the study and had achieved over a 90% accuracy rate when assessing ex vivo images. No other details about the endoscopists’ training or experience performing colonoscopies or using NBI are provided, although in the Discussion, the authors state that the centre had already-established expertise in endoscopy. Histological diagnosis by a clinical pathologist. | | | | | | |
| **Polyp classification system (including histological classification e.g. NICE)** | Not explicitly stated, but assumed to be the simplified NBI International Classification for Endoscopy that the endoscopists were trained in before the study commenced. | | | | | | |
| **Sample size calculation** | Based on preliminary data collected using the 180 colonoscope, a mean of 0.86 polyps and 0.51 adenomas per patient would need to be identified. This meant that it was likely that 59% of the polyps would be neoplastic. Previously collected data suggested NBI has a sensitivity of 84%, a specificity of 75% and an overall accuracy of 80%. It was therefore calculated that 230 polyps per group (460 polyps in total) would be needed to detect an increase in accuracy from 80% to 90% between the two colonoscopy procedures, which would provide a power of 80% to find a statistical significance level of 5%. | | | | | | |
| **Results – NBI using 180 colonoscope to characterise polyps sized ≤5mm (n = 310)** | | | | | | | |
|  | **Adenomatous polyps on histopathology\*** | | **Hyperplastic polyps on histopathology\*\*** | | | **Total** | |
| **Index test positive** | (a) 120 | | (b) 35\*\*\*\* | | | 155 | |
| **Index test negative** | (c) 31\*\*\*\* | | (d) 124 | | | 155\*\*\*\* | |
| **Total** | 151\*\*\* | | 159 | | | 310 | |
| **Accuracy** ([a+d]/[a+b+c+d]) | 79% (244 of 310 polyps correctly diagnosed; CIs not reported) | | | | | | |
| ***Diagnosis*** | | **Value** | | **95% CI** | | | |
| **Clinical sensitivity a / (a + c)** | | 79% | | 72.14% to 85.60%\*\*\*\* | | | |
| **Clinical specificity d / (b + d)** | | 78% | | 70.74% to 84.16%\*\*\*\* | | | |
| **PPV a / (a + b)** | | 77% | | 70.02% to 83.74%\*\*\*\* | | | |
| **NPV d / (c + d)** | | 80% | | 72.83% to 85.99%\*\*\*\* | | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 3.61\*\*\*\* | | 2.66 to 4.89\*\*\*\* | | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.26\*\*\*\* | | 0.19 to 0.36\*\*\*\* | | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 13.714\*\*\*\* | | 7.955 to 23.644\*\*\*\* | | | |
| Reviewer’s calculations of accuracy, sensitivity, specificity, PPV and NPV agree with those reported in the paper. Note: CIs not reported in the paper.  \* Neoplastic polyps.  \*\* Non-neoplastic polyps.  \*\*\* Table 7 (p. 1080) states that 151 polyps were neoplastic, while Table 5 (p. 1078) states that 152 polyps were neoplastic.  \*\*\*\* Calculated by reviewer. | | | | | | | |
| **Results – NBI using 180 colonoscope to characterise polyps sized ≤5mm located in the rectosigmoid (n = 125)** | | | | | | | |
|  | **Adenomatous polyps on histopathology\*** | | **Hyperplastic polyps on histopathology\*\*** | | | | **Total** |
| **Index test positive** | (a) 21 | | (b) 16\*\*\* | | | | 37 |
| **Index test negative** | (c) 4\*\*\* | | (d) 84 | | | | 88\*\*\* |
| **Total** | 25 | | 100\*\*\* | | | | 125 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 84% (105 of 125 polyps accurately diagnosed; CIs not reported) | | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 84% | | | 63.92% to 95.46%\*\*\* | | |
| **Clinical specificity d / (b + d)** | | 84% | | | 75.32% to 90.57%\*\*\* | | |
| **PPV a / (a + b)** | | 57% | | | 39.49% to 72.90%\*\*\* | | |
| **NPV d / (c + d)** | | 95% | | | 88.77% to 98.75%\*\*\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 5.25\*\*\* | | | 3.25 to 8.49\*\*\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.19\*\*\* | | | 0.08 to 0.47\*\*\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 27.563\*\*\* | | | 8.339 to 91.096\*\*\* | | |
| Reviewer’s calculations of accuracy, sensitivity, specificity, PPV and NPV agree with those reported in the paper. Note: CIs not reported in the paper.  \* Neoplastic polyps.  \*\* Non-neoplastic polyps.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results – High confidence predictions using NBI 180 colonoscope to characterise polyps sized ≤5mm (n = 257)** | | | | | | | |
|  | **Adenomatous polyps on histopathology\*** | | **Hyperplastic polyps on histopathology\*\*** | | | | **Total** |
| **Index test positive** | (a) 102 | | (b) 22\*\*\* | | | | 124 |
| **Index test negative** | (c) 24\*\*\* | | (d) 109 | | | | 133\*\*\* |
| **Total** | 126 | | 131\*\*\* | | | | 257 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 82% (211 of 257 polyps accurately diagnosed) | | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 80.95%\*\*\* | | | 73.00% to 87.40%\*\*\* | | |
| **Clinical specificity d / (b + d)** | | 83.21%\*\*\* | | | 75.69% to 89.17%\*\*\* | | |
| **PPV a / (a + b)** | | 82% | | | 74.38% to 88.53%\*\*\* | | |
| **NPV d / (c + d)** | | 82% | | | 74.35% to 88.08%\*\*\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 4.82\*\*\* | | | 3.26 to 7.12\*\*\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.23\*\*\* | | | 0.16 to 0.33\*\*\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 21.057\*\*\* | | | 11.121 to 39.871\*\*\* | | |
| 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.*  Reviewer’s calculations of accuracy, PPV and NPV agree with those reported in the paper. Note: CIs not reported in the paper.  \* Neoplastic polyps.  \*\* Non-neoplastic polyps.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results – Low confidence predictions using NBI 180 colonoscope to characterise polyps sized ≤5mm (n = 53)** | | | | | | | |
|  | **Adenomatous polyps on histopathology\*** | | **Hyperplastic polyps on histopathology\*\*** | | | | **Total** |
| **Index test positive** | (a) 18 | | (b) 13\*\*\* | | | | 31 |
| **Index test negative** | (c) 7\*\*\* | | (d) 15 | | | | 22\*\*\* |
| **Total** | 25 | | 28\*\*\* | | | | 53 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 62% (33 of 53 polyps accurately diagnosed) | | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 72.00%\*\*\* | | | 50.61% to 87.93%\*\*\* | | |
| **Clinical specificity d / (b + d)** | | 53.57%\*\*\* | | | 33.87% to 72.49%\*\*\* | | |
| **PPV a / (a + b)** | | 58% | | | 39.08% to 75.45%\*\*\* | | |
| **NPV d / (c + d)** | | 68% | | | 45.13% to 86.14%\*\*\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 1.55\*\*\* | | | 0.97 to 2.47\*\*\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.52\*\*\* | | | 0.26 to 1.07\*\*\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 2.967\*\*\* | | | 0.943 to 9.335\*\*\* | | |
| Reviewer’s calculations of accuracy, PPV and NPV agree with those reported in the paper. Note: CIs not reported in the paper.  \* Neoplastic polyps.  \*\* Non-neoplastic polyps.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Results – High confidence predictions using NBI 180 colonoscope to characterise polyps sized ≤5mm located in the rectosigmoid (n = 104)** | | | | | | | |
|  | **Adenomatous polyps on histopathology\*** | | **Hyperplastic polyps on histopathology\*\*** | | | | **Total** |
| **Index test positive** | (a) 18 | | (b) 7\*\*\* | | | | 25 |
| **Index test negative** | (c) 3\*\*\* | | (d) 76 | | | | 79\*\*\* |
| **Total** | 21 | | 83\*\*\* | | | | 104 |
| **Accuracy** ([a+d]/[a+b+c+d]) | 90% (94 of 104 polyps accurately diagnosed) | | | | | | |
| ***Diagnosis*** | | **Value** | | | **95% CI** | | |
| **Clinical sensitivity a / (a + c)** | | 85.71%\*\*\* | | | 63.66% to 96.95%\*\*\* | | |
| **Clinical specificity d / (b + d)** | | 91.57\*\*\* | | | 83.39% to 96.54%\*\*\* | | |
| **PPV a / (a + b)** | | 72% | | | 50.61% to 87.93%\*\*\* | | |
| **NPV d / (c + d)** | | 96% | | | 89.30% to 99.21%\*\*\* | | |
| **Positive likelihood ratio [sensitivity/(1-specificity)]** | | 10.16\*\*\* | | | 4.90 to 21.09\*\*\* | | |
| **Negative likelihood ratio [(1-sensitivity)/specificity]** | | 0.16\*\*\* | | | 0.05 to 0.45\*\*\* | | |
| **Diagnostic odds ratio (a x d)/(b x c)** | | 65.143\*\*\* | | | 15.53 to 276.824\*\*\* | | |
| Reviewer’s calculations of accuracy, PPV and NPV agree with those reported in the paper. Note: CIs not reported in the paper.  \* Neoplastic polyps.  \*\* Non-neoplastic polyps.  \*\*\* Calculated by reviewer. | | | | | | | |
| **Interpretability of test** | | Not reported | | | | | |
| **Inter-observer agreement** | | Not reported | | | | | |
| **Intra-observer agreement** | | Not reported | | | | | |
| **Test acceptability (patients / clinicians)** | | Not reported | | | | | |
| **Adverse events** | | Not reported | | | | | |
| **High confidence optical diagnosis** | | 257/310 (82.9%) diminutive polyps in the NBI 180 arm were predicted with high confidence. 104 of the 125 (83.2%) diminutive polyps located in the rectosigmoid were predicted with high confidence. %s calculated by reviewer. 2x2 tables shown above. | | | | | |
| **Low confidence optical diagnosis** | | 53/310 (17.1%) diminutive polyps in the NBI 180 arm were predicted with low confidence. % calculated by reviewer. 2x2 table shown above. The proportion of diminutive polyps located in the rectosigmoid which were predicted with low confidence is not reported. | | | | | |
| **Number of polyps designated to be left in place** | | Not reported | | | | | |
| **Number of polyps designated to be resected and discarded** | | Not reported | | | | | |
| **Number of polyps designated for resection and histopathological examination** | | Not reported | | | | | |
| **Recommended surveillance interval** | | Assignment of surveillance intervals was based on the number and size of the adenomas: I, 0 adeomas (10 years); II, 1 to 2 adenomas <10mm (5 years); III, 3 to 5 adenomas <10mm or any adenomas 10 to 20mmm (3 years); IV, >5 adenomas or any adenoma >20mm (3 months to 1 year).  Agreement between histopathology and NBI 180 predictions, all polyps: 221/264 patients (84%, CIs 79% to 88%). Under NBI 27 patients would have returned earlier and 16 later than assigned by histopathology.  Agreement between histopathology and NBI 180 predictions, when assignment of surveillance interval for polyps sized ≤5mm predicted with high confidence is made with NBI 180, while histopathology is used for assignment of surveillance intervals in all other cases (as per the Preservation and Incorporation of Valuable endoscopic Innovations guidelines): 250/264 patients (95%, CIs 91% to 97%). Under NBI 5 patients would have returned earlier and 9 later than assigned by histopathology. | | | | | |
| **Length of time to perform the colonoscopy** | | Insertion time, min: mean (SD) 6.6 (3.8); median (IQR) 5.7 (3.9 to 8.2).  Withdrawal time, min: mean (SD) 16.1 (7.3); median (IQR) 14.5 (11.0 to 19.2).  Total procedure time, min: mean (SD) 22.7 (8.3); median (IQR) 20.8 (17.1 to 27.0).  NB Results for all procedures and not just those in which diminutive polyps were identified. | | | | | |
| **Number of outpatient appointments** | | Not reported | | | | | |
| **Health related quality of life** | | Not reported | | | | | |
| **Colorectal cancer** | | Not reported | | | | | |
| **Mortality** | | Not reported | | | | | |

**Critical appraisal criteria** (based on Reitsma et al.50 adaptation of the QUADAS Tool51)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Item** | **Description** | **Judgement** |
| 1 | Was the spectrum of patients representative of the patients who will receive the test in practice? | Few details provided about the indications for the colonoscopy. Of the patients, 46% were undergoing routine colonoscopy, 43% surveillance colonoscopy and 10% diagnostic colonoscopy – patients were described as being ‘at average risk’ (not further defined). | Yes |
| 2 | Is the reference standard likely to classify the target condition correctly? | Histopathology is considered to be the gold standard | Yes |
| 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? | The real time virtual chromoendoscopy assessment and the polyp resection for histopathological analysis would be performed at the same time (i.e. during the same colonoscopy). | Yes |
| 4 | Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? | 10 diminutive polyps were not assessed by histopathology and it is unclear whether another polyp was sent for histopathological examination. | No |
| 5 | Did patients receive the same reference standard irrespective of the index test result? | Although 10 diminutive polyps were not assessed by histopathology there is no indication that they received a different reference standard or that it was the NBI result that caused them to be omitted from histopathological assessment. | Yes |
| 6 | Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)? |  | Yes |
| 7 | Were the reference standard results interpreted without knowledge of the results of the index test? | It is unclear if the pathologist had knowledge of the colonoscopy result, as the authors do not reported if s/he was blinded to this. | Unclear |
| 8 | Were the index test results interpreted without knowledge of the results of the reference standard? | The reference standard results could not be known at the time of the index test result. | Yes |
| 9 | Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? |  | Yes |
| 10 | Were uninterpretable/ intermediate test results reported? | The authors do not state if there were any uninterpretable results. Not all patients who were randomised completed the study, so it is possible that there might have been uninterpretable test results. | Unclear |
| 11 | Were withdrawals from the study explained? |  | Yes |

yes / no / unclear

|  |  |
| --- | --- |
| Reference list of the included paper(s) checked? Yes/no | Yes – no additional relevant studies cited |

|  |
| --- |
| Summary reviewer’s comments |
| This study was carried out at one centre in the USA with established expertise in endoscopy and included a large number of diminutive polyps. It is unclear how generalisable these results are to practice (and the patient population of interest in this appraisal) as few details are provided about the patient population included in the study. Seven endoscopists performed the colonoscopies, meaning that the results came from a range of endoscopists, which enhances the generalisability of the findings. The authors comment, though, that the accuracy rates seen in established endoscopy centres may not apply to broader practice, so it is possible that the accuracy rates found in this study may not be found in other settings or among less experienced endoscopists. |

Appendix Table of excluded studies with rationale

|  |  |
| --- | --- |
| **Authors and study reference** | **Reason for exclusion a** |
| Adler A, Aschenbeck J, Yenerim T, Mayr M, Aminalai A, Drossel R, et al. Narrow-band versus white-light high definition television endoscopic imaging for screening colonoscopy: a prospective randomized trial. *Gastroenterology* 2009;136(2):410-6.e1; quiz 715 | Outcomes |
| Aminalai A, Roesch T, Aschenbeck J, Mayr M, Drossel R, Schroeder A, et al. Live Image Processing Does Not Increase Adenoma Detection Rate During Colonoscopy: A Randomized Comparison Between FICE and Conventional Imaging (Berlin Colonoscopy Project 5, BECOP-5). *American Journal of Gastroenterology* 2010;105(11):2383-88. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Bade K, MacPhail ME, Johnson CS, Kahi CJ, Rex DK. New colonoscope technology: impact on image capture and quality and on confidence and accuracy of endoscopy-based polyp discrimination. *Endoscopy* 2014;46(3):172-8. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Banks MR, Haidry R, Adil Butt M, Whitley L, Stein J, Langmead L, et al. High resolution colonoscopy in a bowel cancer screening program improves polyp detection. *World Journal of Gastroenterology* 2011;17(38):4308-13. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Bowman EA, Pfau PR, Mitra A, Reichelderfer M, Gopal DV, Hall BS, et al. High Definition Colonoscopy Combined with i-SCAN Imaging Technology Is Superior in the Detection of Adenomas and Advanced Lesions Compared to High Definition Colonoscopy Alone. *Diagnostic & Therapeutic Endoscopy* 2015;2015:167406. | Outcomes |
| Broek FJ, Fockens P, Eeden S, Kara MA, Hardwick JC, Reitsma JB, et al. Clinical evaluation of endoscopic trimodal imaging for the detection and differentiation of colonic polyps. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2009;7(3):288-95 | Intervention (used magnification) |
| Buchner AM, Shahid MW, Heckman MG, Krishna M, Ghabril M, Hasan M, et al. Comparison of probe-based confocal laser endomicroscopy with virtual chromoendoscopy for classification of colon polyps. *Gastroenterology* 2010;138(3):834-42 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Burgess NG, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, et al. Sa1565 Dysplasia Impedes the Correct Endoscopic Prediction of Large Sessile Serrated Polyp Histology in a Multicentre Prospective Cohort. *Gastrointest Endosc.* 2015;81(5):AB263-AB4. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Bustamente M, Puchades L, Ponce M, Arguello L, Pons V. Olympus “Near Focus” Narrow Band Imaging (Nbi) Vs Conventional Nbi For In Vivo Endoscopic Histology Of Colonic Polyps: A Randomized Controlled Trial. UEG Week 2014 Poster Presentations; October 1, 2014; Amsterdam: *United European Gastroenterology Journal*; 2014. p. A132-A605. | Abstract- insufficient details |
| Cha JM, Lee JI, Joo KR, Jung SW, Shin HP. A prospective randomized study on computed virtual chromoendoscopy versus conventional colonoscopy for the detection of small colorectal adenomas. *Digestive Diseases and Sciences* 2010;55(8):2357-64 | Outcomes |
| Chan JL, Lin L, Feiler M, Wolf AI, Cardona DM, Gellad ZF. Comparative effectiveness of i-SCAN (TM) and high-definition white light characterizing small colonic polyps. *World Journal of Gastroenterology* 2012;18(41):5905-11 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Chernolesskiy A, Swain D, Lee JC, Corbett GD, Cameron EA. Comparison of Pentax HiLine and Olympus Lucera systems at screening colonoscopy. *World Journal of Gastrointestinal Endoscopy* 2013;5(2):62-6 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Chiu H-M, Chang L-C, Shun C-T, Wu M-S, Wang H-P. Current management of diminutive colorectal polyps in Taiwan. *Digestive Endoscopy* 2014;26:64-67. | Intervention |
| Chung SJ, Kim D, Song JH, Kang HY, Chung GE, Choi J, et al. Comparison of detection and miss rates of narrow band imaging, flexible spectral imaging chromoendoscopy and white light at screening colonoscopy: a randomised controlled back-to-back study. *Gut* 2014;63(5):785-91. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Chung SJ, Kim D, Song JH, Park MJ, Kim YS, Kim JS, et al. Efficacy of computed virtual chromoendoscopy on colorectal cancer screening: a prospective, randomized, back-to-back trial of Fuji Intelligent Color Enhancement versus conventional colonoscopy to compare adenoma miss rates. *Gastrointestinal Endoscopy* 2010;72(1):136-42 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Coe SG, Thomas C, Crook J, Ussui V, Diehl N, Wallace MB. Colorectal surveillance interval assignment based on in vivo prediction of polyp histology: impact of endoscopic quality improvement program. *Gastrointestinal Endoscopy* 2012;76(1):118-25.e1 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Gilani N, Stipho S, Panetta JD, Petre S, Young MA, Ramirez FC. Polyp detection rates using magnification with narrow band imaging and white light. *World Journal of Gastrointestinal Endoscopy* 2015;7(5):555-62 | Intervention (not real-time assessment) |
| Gross SA, Buchner AM, Crook JE, Cangemi JR, Picco MF, Wolfsen HC, et al. A comparison of high definition-image enhanced colonoscopy and standard white-light colonoscopy for colorectal polyp detection. *Endoscopy* 2011;43(12):1045-51. | Intervention (no real-time characterisation) |
| Hoffman A, Loth L, Rey JW, Rahman F, Goetz M, Hansen T, et al. High definition plus colonoscopy combined with i-scan tone enhancement vs. high definition colonoscopy for colorectal neoplasia: A randomized trial. *Digestive & Liver Disease* 2014;46(11):991-6 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Hoffman A, Sar F, Goetz M, Tresch A, Mudter J, Biesterfeld S, et al. High definition colonoscopy combined with i-Scan is superior in the detection of colorectal neoplasias compared with standard video colonoscopy: a prospective randomized controlled trial. *Endoscopy* 2010;42(10):827-33. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Hong SN, Choe WH, Lee JH, Kim SI, Kim JH, Lee TY, et al. Prospective, randomized, back-to-back trial evaluating the usefulness of i-SCAN in screening colonoscopy. *Gastrointestinal Endoscopy* 2012;75(5):1011-21.e2 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Inoue T, Murano M, Murano N, Kuramoto T, Kawakami K, Abe Y, et al. Comparative study of conventional colonoscopy and pan-colonic narrow-band imaging system in the detection of neoplastic colonic polyps: a randomized, controlled trial. *Journal of Gastroenterology* 2008;43(1):45-50 | Intervention (detection only, no characterisation) |
| Kąkol D, Frączek M, Banaszkiewicz A, Pertkiewicz J. Narrow-band imaging and white-light endoscopy for detection of colorectal polyps: a randomized study. *Polskie Archiwum Medycyny Wewn?trznej* 2013;123(10):519-25 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Kaltenbach T, Sano Y, Friedland S, Soetikno R. American gastroenterological association (AGA) institute technology assessment on image-enhanced endoscopy. *Gastroenterology* 2008;134(1):327-40 | Study design |
| Kim JJ, Hong KS, Kim JS, Jung HC. A Randomized Controlled Clinical Study Comparing the Diagnostic Accuracy of the Histologic Prediction for Colorectal Polyps Depending on the Use of Either Magnified or Nonmagnified Narrow Band Imaging. *Clinical Endoscopy* 2015;48(6):528-33. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Kim WJ, Park SY, Park I, Lee WJ, Park J, Chon N, et al. Increased Detection of Colorectal Polyps in Screening Colonoscopy Using High Definition i-SCAN Compared with Standard White Light. *Clinical Endoscopy* 2016;49(1):69-75. | Intervention (detection only, no characterisation) |
| Kim YS, Kim D, Chung SJ, Park MJ, Shin CS, Cho SH, et al. Differentiating small polyp histologies using real-time screening colonoscopy with Fuji Intelligent Color Enhancement. *Clinical Gastroenterology & Hepatology* 2011;9(9):744-49.e1. | Intervention (used magnification) |
| Kominami Y, Yoshida S, Tanaka S, Sanomura Y, Hirakawa T, Raytchev B, et al. Computer-aided diagnosis of colorectal polyp histology by using a real-time image recognition system and narrow-band imaging magnifying colonoscopy. *Gastrointestinal Endoscopy* 2016;83(3):643-9 | Intervention (used magnification) |
| Kuiper T, Broek FJ, Naber AH, Soest EJ, Scholten P, Mallant-Hent R, et al. Endoscopic trimodal imaging detects colonic neoplasia as well as standard video endoscopy. *Gastroenterology* 2011;140(7):1887-94 | Intervention (used magnification) |
| Kuiper T, Marsman WA, Jansen JM, van Soest EJ, Haan YC, Bakker GJ, et al. Accuracy for optical diagnosis of small colorectal polyps in nonacademic settings. *Clinical Gastroenterology & Hepatology* 2012;10(9):1016-20 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Kuiper T, van den Broek FJ, van Eeden S, Fockens P, Dekker E. Feasibility and accuracy of confocal endomicroscopy in comparison with narrow-band imaging and chromoendoscopy for the differentiation of colorectal lesions. *American Journal of Gastroenterology* 2012;107(4):543-50 | Patient group (polyposis syndromes included) |
| Kumar S, Fioritto A, Mitani A, Desai M, Gunaratnam N, Ladabaum U. Optical biopsy of sessile serrated adenomas: do these lesions resemble hyperplastic polyps under narrow-band imaging? *Gastrointestinal Endoscopy* 2013;78(6):902-9 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Kuruvilla N, Paramsothy R, Gill R, Remedios M, Selby WS, Kaffes AJ. A prospective dual centre evaluation of narrow band imaging (NBI) with a fixed zoom function in real time prediction of polyp histology: Can we resect and discard? *Journal of Gastroenterology and Hepatology (Australia)* 2014;29((Suppl. 2)) | Intervention (used magnification) |
| Kuruvilla N, Paramsothy R, Gill R, Selby WS, Remedios ML, Kaffes AJ. A prospective dual-center proof-of-principle study evaluating the incremental benefit of narrow-band imaging with a fixed zoom function in real-time prediction of polyp histology. Can we resect and discard? *Gastrointestinal Endoscopy* 2015;82(2):362-9. | Intervention (used magnification) |
| Lapalus MG, Helbert T, Napoleon B, Rey JF, Houcke P, Ponchon T. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy. 2006;38(5):444-8. | Intervention |
| Ljubicic N, Kujundzic M, Banic M, Roic G. The role of standard videochromocolonoscopy in distinguishing adenomatous from nonadenomatous diminutive colorectal polyps. *Acta Clinica Croatica* 2001;40(3):197-201 | Intervention |
| Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, et al. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. *Endoscopy* 2004;36(12):1094-8. | Intervention (used magnification) |
| Mayr M, Treszl A, Balzer K, Wegscheider K, Aschenbeck J, Aminalai A, et al. Endoscopic versus histological characterisation of polyps during screening colonoscopy Guido Schachschal,1. Gut. 2014;63(3):458-65. | Outcomes |
| Neumann H, Vieth M, Guenther C, Neurath MF. Improved detection of proximal colon adenomas with i-scan in comparison to high-definition white light endoscopy. *Journal of Gastroenterology and Hepatology* 2014;29:9-10 | Outcomes |
| Neumann H, Vieth M, Guenther C, Neurath MF. High-definition endoscopy with i-scan allows in vivo characterization of distal colorectal polyps according to the ASGE PIVI statement. *Journal of Gastroenterology and Hepatology* 2014;29:9-9 | Abstract- insufficient details |
| Notaristefano C, Viale E, Di Marco B, Maselli R, Testoni PA. High definition colonoscopy with I-SCAN and digital chromoendoscopy in the pit pattern analysis: A single center experience. *Gastrointestinal Endoscopy* 2015;1):AB384. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Paramsothy R, Kuruvilla NA, Gill RS, Selby W, Remedios M, Kaffes AJ. A prospective dual centre evaluation of narrow band imaging (NBI) with a fixed zoom function in real time prediction of polyp histology. Can we resect and discard? *Gastrointestinal Endoscopy* 2015;1):AB267-AB68. | Intervention (used magnification) |
| Patel SG, Schoenfeld P, Bansal A, Hosford L, Myers A, Wilson RH, Craft J, Ahnen D, Rastogi A, Wani, S.). Low prevalence of advanced histological features in diminutive colon polyps: Results from a prospective multicenter study evaluating real-time characterization of diminutive colorectal polyp histology using Narrow Band Imaging (NBI). Gastrointestinal Endoscopy 2016 1): AB146 | Outcomes |
| Pohl J, Lotterer E, Balzer C, Sackmann M, Schmidt KD, Gossner L, et al. Computed virtual chromoendoscopy versus standard colonoscopy with targeted indigocarmine chromoscopy: a randomised multicentre trial. *Gut* 2009;58(1):73-8. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Rajasekhar PT, Mason J, Wilson A, Close H, Rutter MD, Saunders B, et al. Narrow Band Imaging Optical Diagnosis Of Small Colorectal Polyps In Routine Clinical Practice: The Detect Inspect Characterise Resect And Discard (Discard 2) Study. UEG Week 2015 Oral Presentations; October 1, 2015; Barcelona: *United European Gastroenterology Journal*; 2015. p. 1-145. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Rajasekhar PT, Mason J, Wilson A, Close H, Rutter M, Saunders B, et al. Detect inspect characterise resect and discard 2: Are we ready to dispense with histology? *Gut* 2015;64:A13 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Ramirez-Ramirez MA, Mejia Cuan LA, Martinez C, Zamorano-Orozco Y, Vieyra SC. Prediction of colorectal polyp pathologic lesions with high definition and virtual chromoendoscopy with I-SCAN 2 in Real time; A prospective study. *Gastrointestinal Endoscopy* 2015;1):AB265. | Abstract- insufficient details |
| Rastogi A, Early DS, Gupta N, Bansal A, Singh V, Ansstas M, et al. Randomized, controlled trial of standard-definition white-light, high-definition white-light, and narrow-band imaging colonoscopy for the detection of colon polyps and prediction of polyp histology. *Gastrointestinal Endoscopy* 2011;74(3):593-602 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Rees CJ, Rajasekhar PT, Wilson A, Close H, Rutter MD, Saunders BP, et al. Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. *Gut*. 2016. | Intervention (majority of colonoscopies not HD) |
| Rey JF, Tanaka S, Lambert R, Tajiri H. Evaluation of the clinical outcomes associated with EXERA II and LUCERA endoscopes. *Digestive Endoscopy* 2009;21 Suppl 1:S113-20. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Rotondano G, Bianco MA, Sansone S, Prisco A, Meucci C, Garofano ML, et al. Trimodal endoscopic imaging for the detection and differentiation of colorectal adenomas: a prospective single-centre clinical evaluation. *International Journal of Colorectal Disease* 2012;27(3):331-6. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Sakamoto T, Matsuda T, Aoki T, Nakajima T, Saito Y. Time saving with narrow-band imaging for distinguishing between neoplastic and non-neoplastic small colorectal lesions. *Journal of Gastroenterology and Hepatology* 2012;27(2):351-5. | Intervention (used magnification) |
| Sakatani A, Fujiya M, Tanaka K, Dokoshi T, Fujibayashi S, Ando K, et al. Usefulness of NBI for differentiating colon neoplasms from non-neoplasms: Based on results of our institutional experience and a meta-analysis of comparative studies. *Gastrointestinal Endoscopy* 2014;1):AB442 | Intervention (not real-time assessment) |
| Seref Koksal A, Yildiz H, Taskiran I, Turhan N, Oztas E, Torun S, et al. Low magnification narrow band imaging by inexperienced endoscopists has a high accuracy in differentiation of colon polyp histology. Clinics and research in hepatology and gastroenterology. 2014;38(6):763-9. | Intervention (colonoscope not HD) |
| Sharma P, Frye J, Frizelle F. Accuracy of visual prediction of pathology of colorectal polyps: how accurate are we? *ANZ Journal of Surgery* 2014;84(5):365-70. | Intervention |
| Singh R, Cheong KL, Yeap SP, Ovenden A, Ruszkiewicz A, Dy F, Ramchandani M, Goh KL, Ho SH, Rerknimitr R, Ang TL, Seo DW, Jung HY, Wang HP, Menon J, Ong EG, Lee CT, Chiu PW, Lau JY. A prospective multicentre study assessing the utility of narrow band imaging with dual focus magnification in differentiating colorectal Neoplasia using the nice and modified sano's classification. Gastrointestinal Endoscopy 2016 1): AB152. | Intervention (used magnification) |
| Singh R, Jayanna M, Navadgi S, Ruszkiewicz A, Saito Y, Uedo N. Narrow-band imaging with dual focus magnification in differentiating colorectal neoplasia. *Digestive Endoscopy* 2013;25 Suppl 2:16-20. | Intervention (used magnification) |
| Song LMWK, Adler DG, Conway JD, Diehl DL, Farraye FA, Kantsevoy SV, et al. Narrow band imaging and multiband imaging. *Gastrointestinal Endoscopy* 2008;67(4):581-89. | Study design |
| Su MY, Hsu CM, Ho YP, Chen PC, Lin CJ, Chiu CT. Comparative study of conventional colonoscopy, chromoendoscopy, and narrow-band imaging systems in differential diagnosis of neoplastic and nonneoplastic colonic polyps. *American Journal of Gastroenterology* 2006;101(12):2711-6 | Intervention (not real-time) |
| Szura M, Pasternak A, Bucki K, Urbanczyk K, Matyja A. Two-stage optical system for colorectal polyp assessments. *Surgical Endoscopy* 2016;30(1):204-14. | Intervention (used magnification) |
| Takeuchi Y, Hanafusa M, Kanzaki H, Ohta T, Hanaoka N. Proposal of a new 'resect and discard' strategy using magnifying narrow band imaging: pilot study of diagnostic accuracy. *Digestive Endoscopy* 2014;26 Suppl 2:90-7 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Takeuchi Y, Hanafusa M, Kanzaki H, Ohta T, Hanaoka N, Yamamoto S, et al. An alternative option for "resect and discard" strategy, using magnifying narrow-band imaging: a prospective "proof-of-principle" study. *Journal of Gastroenterology* 2015;50(10):1017-26. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Tischendorf JJ, Schirin-Sokhan R, Streetz K, Gassler N, Hecker HE, Meyer M, et al. Value of magnifying endoscopy in classifying colorectal polyps based on vascular pattern. *Endoscopy* 2010;42(1):22-7. | Intervention (not real-time) |
| Togashi K, Osawa H, Koinuma K, Hayashi Y, Miyata T, Sunada K, et al. A comparison of conventional endoscopy, chromoendoscopy, and the optimal-band imaging system for the differentiation of neoplastic and non-neoplastic colonic polyps. *Gastrointestinal Endoscopy* 2009;69(3 Pt 2):734-41. | Intervention (used magnification) |
| van Dam L, Wijkerslooth TR, Haan MC, Stoop EM, Bossuyt PM, Fockens P, et al. Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial. *Endoscopy* 2013;45(3):182-8. | Intervention |
| Weigt J, Kandulski A, Malfertheiner P. New generation flexible spectral imaging color enhancement is useful to predict histology of small colorectal polyps. Gastrointest Endosc. 2014; 79(5 suppl. 1):Ab434 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Yeap SP, Singh R, Ovenden A, Ruszkiewicz A, Lau JY, Rerknimitr R, et al. A randomised controlled trial comparing the modified Sano's versus the nice classifications using narrow band imaging with near focus magnification in differentiating colorectal polyps. *Gastrointestinal Endoscopy* 2015;81(5 suppl. 1):Ab259-ab60 | Intervention (used magnification) |
| Yoshida Y, Matsuda K, Sumiyama K, Kawahara Y, Yoshizawa K, Ishiguro H, et al. A randomized crossover open trial of the adenoma miss rate for narrow band imaging (NBI) versus flexible spectral imaging color enhancement (FICE). *International Journal of Colorectal Disease* 2013;28(11):1511-6 | Comparator (histology not compared to VCE separately for polyps ≤5mm) |
| Zhou QJ, Yang JM, Fei BY, Xu QS, Wu WQ, Ruan HJ. Narrow-band imaging endoscopy with and without magnification in diagnosis of colorectal neoplasia. *World Journal of Gastroenterology* 2011;17(5):666-70. | Comparator (histology not compared to VCE separately for polyps ≤5mm) |

a The first item in the flowchart that the reviewers agreed would be a reason for exclusion was recorded as the primary reason for exclusion.

Appendix Ongoing studies

Table 67 and Table 68 list the 19 potentially relevant ongoing studies identified from searches of clinical trials databases and identified from conference abstracts for recently complete and ongoing studies that have not been published in full yet. Reviewers decided during study selection that it was unclear if these conference abstracts met the inclusion criteria for the review. This was due to limitations in the information reported. For example, often the population was unclear, it was unclear whether optical diagnosis was performed using magnification and high definition equipment, and for studies not limited to diminutive polyps, it was unclear whether results will be presented separately for diminutive polyps only.

Table Ongoing studies identified from the searches for ongoing trials

|  |  |  |
| --- | --- | --- |
| **Study identifier, location** | **Study title** | **Estimated completion date and enrollment** |
| NCT02407925  The Netherlands | Implementation of optical diagnosis for diminutive polyps amongst accredited endoscopists for the Dutch bowel cancer screening program: training and long-term quality assurance (DISCOUNT2) | January 2017  N = 1500 |
| NCT02516748  Republic of Korea | Prospective study of real-time diagnosis of colorectal polyps using narrow-band imaging: Gangnam-ReaDi Study | August 2016  N = 5000 |

Table Identified conference abstracts reporting recently complete or ongoing studies not yet published in full

| **Reference** | **Title** |
| --- | --- |
| Belderbos 2015150 | The accuracy of real-time probe based confocal LASER endomicroscopy for differentiation of colorectal polyps during colonoscopy |
| Kaltenbach 2014151 | Gastroenterology trainees can perform real time optical diagnosis of diminutive colorectal polyps using narrow band imaging |
| Kheir 2016152 | Optical diagnosis of diminutive colorectal polyps by non-academic general gastroenterologists using non-magnifying narrow band imaging (NBI): A prospective study |
| Klein 2014153 | Computerized, image analysis of diminutive polyps during colonoscopy-preliminary results of a feasibility study |
| Lee154 | Learning curve for optical biopsy using narrow band imaging-can real-time training improve accuracy? |
| Lee 2015155 | Learning curve for optical biopsy using narrow band imaging (NBI) - Can real-time training improve accuracy? |
| Madacsy 2015156 | Diagnostic Value Of Fujinon Intelligent Color Enhancement (Fice) Technology With And Without Magnificantion To Differentiate Between Hyperplastic And Adenomatous Lesions According To The Nice Classification - A Prospective, Randomized, Controlled Study |
| Maimone 2015157 | Real-time biopsy of colorectal polyps = 6 mmusing fice, I-scan and NBI technologies: Experience of a young endoscopist |
| Neumann 2015158 | Development and validation of a simple classification system for in vivo diagnosis of colorectal polyps using digital chromoendoscopy - The visible study |
| Paggi 2014159 | Is it really so easy to learn histologic characterization of diminutive polyps by narrow band imaging? Preliminary results of endoscopists' and nurses' performances. |
| Rastogi 2014160 a | Performance of gastroenterology (GI) trainees in real-time characterization of diminutive polyp (DP) histology with narrow band imaging (NBI)-results from a prospective trial. |
| Rastogi 2014161 a | Prediction time for characterizing diminutive (% 5mm) polyp (DP) histology with NBI during colonoscopy is a marker for high confidence (HC) diagnosis and accuracy |
| Rastogi 2014162 a | Gastroenterology (GI) trainees can achieve the PIVI benchmarks for real-time characterization of the histology of diminutive (% 5mm) polyps (DP) - A prospective study |
| Rocha 2014163 | In vivo diagnosis of colorectal polyps by GI endoscopists using HD narrow-band imaging |
| Staiano 2016164 | High-definition colonoscopy using i-scan in morphological characterization and real-time histological prediction of colonic neoplastic superficial lesion. A single italian center pilot study, preliminary results |
| Vleugels 2016 165 | Incorporating sessile serrated polyps in optical diagnosis of diminutive polyps: What are the implications for the PIVI thresholds? |
| Xu 2015166 | Significance of Endoscopic Mucosal Surface Features in Diagnosing Colorectal Polyps |

a These references are possibly linked to the Gupta 2012 study69 included in this review, but this is not clear.

Appendix Studies excluded from the systematic review of cost-effectiveness studies

|  |  |
| --- | --- |
| Authors and study reference | Reason for exclusion |
| Longcroft-Wheaton GR, Higgins B, Bhandari P. Flexible spectral imaging color enhancement and indigo carmine in neoplasia diagnosis during colonoscopy: a large prospective UK series (Structured abstract). *European Journal of Gastroenterology and Hepatology* 2011;23(10):903-11. | Outcome |
| Ignjatovic A, East JE, Suzuki N, Vance M, Guenther T, Saunders BP. Optical diagnosis of small colorectal polyps at routine colonoscopy (Detect InSpect ChAracterise Resect and Discard; DISCARD trial): a prospective cohort study. *Lancet Oncology* 2009;10(12):1171-8. | Intervention / outcome |
| Chandran S, Parker F, Lontos S, Vaughan R, Efthymiou M. Can we ease the financial burden of colonoscopy? Using real-time endoscopic assessment of polyp histology to predict surveillance intervals. *Internal Medicine Journal* 2015;45(12):1293-9. | Outcome |
| Longcroft-Wheaton G, Bhandari P. The cost impact of in vivo diagnosis of diminutive polyps: Experience from a screening endoscopy programme. *Gut* 2011;60:A30. | Abstract |
| Longcroft-Wheaton G, Bhandari P. The cost impact of in vivo diagnosis of diminutive polyps: experience from a screening endoscopy programme. *Gut* 2011;60:A30-A30. | Abstract |
| McGill SK, Soetikno RM, Yokomizo L, Goldhaber-Fiebert JD, Owens D, Kaltenbach T. Optical diagnosis of small colorectal polyps with resect and discard strategy is cost saving. *Gastrointestinal Endoscopy* 2013;1):AB168. | Abstract |
| Solon C, Klausnitzer R, Blissett D, Ihara Z. Economic value of narrow band imaging versus white light endoscopy for the characterization of diminutive polyps in the colon: systematic literature review and cost-consequence model. *J Med Econ* 2016:1-27. | Outcome |
| Patel, S. G., Rastogi A, Schoenfeld, P. et al. "Cost-savings associated with the resect and discard strategy for diminutive polyps: Results from a prospective multicenter study evaluating real-time characterization of diminutive colorectal polyp histology using narrow band imaging (NBI)." Gastrointestinal Endoscopy **1)**: 2016. AB421. | Abstract |

Appendix Data extraction forms of included economic evaluations

|  |  |  |  |
| --- | --- | --- | --- |
| *1* | **Study** | Hassan 2010 | |
| *2* | **Research question** | To calculate the potential savings and drawbacks of a resect and discard policy for diminutive colorectal lesions in a simulated CRC screening cohort | |
| *3* | **Country/setting** | USA, secondary care | |
| *4* | **Funding source** | The funding source of the study is not reported. | |
| *5* | **Analysis type** | Cost effectiveness analysis | |
| *6* | **Study type** | Markov model with health states for: no colorectal neoplasia, diminutive (<= 5mm), small (6-9mm) or large (>=10 mm) adenomatous polyps; localised, regional, or distant CRC; and CRC related death. | |
| *7* | **Perspective** | Societal | |
| *8* | **Time horizon** | Trial, lifetime. Model cycle length: not stated (assumed to be yearly) | |
| *9* | **Model assumptions** | Resect and discard policy was instituted for all the cases in which a high confidence diagnosis was achieved by NBI. All diminutive polyps in which a high confidence diagnosis was not possible were removed and sent for formal histologic evaluation. | |
| *10* | **Discounting (rate)** | Future costs and life years were discounted at 3% per year | |
| *11* | **Costing year, currency** | Not reported | |
| *12* | **Population** | Hypothetical cohort of 100,000 50 year old persons in United States who underwent a colonoscopy for CRC screening. | |
| *13* | **Intervention(s), comparator(s)** | Narrow band imaging versus colonoscopy versus no screening | |
| *14* | **Intervention effect** | Feasibility refers to rate of high confidence in differentiating between hyperplastic and adenomatous diminutive polys by using NBI without magnification. Feasibility of 84% was assumed as the average of Rex and Ignatovic.  Accuracy was defined as the ability to correctly classify adenomatous (true positive) and hyperplastic (true negative) diminutive polyps.  Sensitivity was 94% and specificity was 89% based upon the studies of Rex, Ignatovic and Rastog, | |
| *15* | **Health state utilities** | HRQoL not included | |
| *16* | **Intervention cost** | The authors assumed that no additional costs were incurred for NBI as current generation colonoscopes include this technology. No additional examination and training time, or any other additional material costs were assumed. Cost of colonoscopy was $630, cost of colonoscopy with polypectomy was $925, pathologic examination was $102. Costs were taken from Medicare reimbursement. | |
| *17* | **Indirect costs** | None listed | |
| *18* | **Results**   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Discounted | **No screening** | **Colonoscopy** | **Colonoscopy with resect and discard** | **Incremental** | **ICER** | | **Cost/person** | $3390 | $3222 | $3197 |  |  | | **Relative efficacy** | - | 51 days / person | 51 days / person |  |  |   When projecting the results on the US population, the undiscounted annual cost saving of colonoscopy screening with the resect and discard policy compared with the standard colonoscopy screening approach was estimated to be $33 million. | | |
| *19* | **Sensitivity analysis**  Probabilistic sensitivity analyses were performed. The 5th and 95th percentiles of the undiscounted costs of the resect and discard policy were $15 million and $54 million. Deterministic sensitivity analyses were conducting, varying all parameters. Those results with most relevance were reported.  The feasibility rate of NBI was varied between 50 and 100% for differentiating between hyperplastic and adenomatous diminutive lesions, and the undiscounted benefit for the US population would be $20 million and $40 million respectively. An increase in the cost of pathology examination from the baseline $102 to $150 resulted in an increase of the undiscounted benefit for the US population from the baseline $33 million to $49 million. | | |
| *20* | **Author’s conclusions** | | A resect and discard strategy for diminutive polyps detected by screening colonoscopy resulted in a substantial economic benefit without an impact on efficacy. |

|  |  |  |  |
| --- | --- | --- | --- |
| *1* | **Study** | Kessler, 2011 | |
| *2* | **Research question** | To quantify the expected costs and outcomes of removing diminutive polyps without subsequent pathologic assessment | |
| *3* | **Country/setting** | USA | |
| *4* | **Funding source** | NIH grant | |
| *5* | **Analysis type** | Cost effectiveness analysis | |
| *6* | **Study type** | Decision tree | |
| *7* | **Perspective** | Not reported, but appears to be from payer perspective | |
| *8* | **Time horizon** | Lifetime. The model has a decision tree for the colonoscopy followed by a long term outcome derived from a discrete event simulation model of CRC screening and surveillance strategies (Ness 2000 ref). | |
| *9* | **Model assumptions** | The two strategies did not have different impacts on the extent of the examination and preparation quality of the colonoscopy; there are no differences between strategies in respect of missed polyps, masses or other lesions; and for the resect and discard strategy the endoscopy would be unable to identify advance histology in adenomas 5mm in size or smaller. | |
| *10* | **Discounting (rate)** | Costs not discounted. Unclear whether benefits discounted (not reported). | |
| *11* | **Costing year, currency** | US $ Costing year 2009. | |
| *12* | **Population** | Patients receiving a colonoscopy at a single-institution tertiary centre who had at least one polyp removed during colonoscopy, irrespective of indication. Population characteristic taken from a database of 10,060 consecutive colonoscopies from 1999 to 2004 | |
| *13* | **Intervention(s), comparator(s)** | No pathological examination of diminutive polyps (resect and discard) vs. submitting all polyps for pathological examination (submit all) | |
| *14* | **Intervention effect** | Endoscopic sensitivity for non-adenoma 90%;  Endoscopic sensitivity for adenoma 90%;  Proportion of diminutive polyps with advanced histology 0.6%;  Pathology sensitivity for large adenoma 100%;  Pathology sensitivity for diminutive and small adenoma 95%;  Pathology sensitivity for non-adenoma 100%. | |
| *15* | **Health state utilities** | Not included | |
| *16* | **Intervention cost** | Costs included for pathology, colonoscopy and colorectal cancer treatment. Cost of sending a polyp to pathology US$103.87, colonoscopy cost: diagnostic US$1329, therapeutic US$2038. Major bleeding cost US$4360, perforation US$13000. Colorectal cancer treatment cost: localized US$51,800, regional US$76,500, distant US$80,000. | |
| *17* | **Indirect costs** | Not included | |
| *18* | **Results**  The submit all strategy results in an incorrect surveillance interval 1.9% of the time, while the resect and discard strategy does so 11.8% of the time, with over half of the patients having only non-adenomatous polyps and scheduled for a 5 year, rather than a 10 year surveillance examination. The cost savings from forgoing pathologic assessment is US$210 per colonoscopy when diminutive polyps are removed, while the additional cost due to the incorrect surveillance interval was US$35.92. The net savings was US$174.01. The number needed to harm because of perforation, major bleed or missed cancer is 7979, i.e., an absolute risk of 0.0125%.  The expected benefit of the submit all strategy was 0.17 days and the cost effectiveness of the submit all strategy compared to the resect and discard was US$377 460 per life year gained. | | |
| *19* | **Sensitivity analysis**  Deterministic sensitivity analyses were conducted for the accuracy of the colonoscopy to detect adenomas and the proportion of diminutive polyps with advanced histology. The sensitivity analyses performed indicate that the error rate in assigning post-polypectomy surveillance intervals is most sensitive to the accuracy of endoscopic assessment of histology and to the proportion of diminutive polyps with advanced histology. | | |
| *20* | **Author’s conclusions** | | Endoscopic diagnosis of polyp histology during colonoscopy and forgoing pathologic examination would result in substantial upfront cost savings. Downstream consequences of the resulting incorrect surveillance intervals appear to be negligible. |

Appendix Data extraction of company’s economic evaluation

**1 Reference**

|  |
| --- |
| Solon (2016), Company submission from Olympus |

**1.1 Health technology**

|  |
| --- |
| Narrow band imaging (NBI) |

**1.2 Interventions and comparators**

What interventions/ strategies were included?

|  |
| --- |
| NBI was compared to high definition white light endoscopy (HD-WLE) |

Was a no treatment/ supportive care strategy included?

|  |
| --- |
| No |

Describe interventions/ strategies

|  |
| --- |
| All patients that enter the model undergo an endoscopy test using either NBI or HD-WLE which results in one or more polyp being identified. |

**1.3 Research question**

What are the stated objectives of the evaluation?

|  |
| --- |
| To compare NBI to HD-WLE (assumed to be the current standard of care in the UK) |

**1.4 Study type** Cost-effectiveness/ cost-utility/ cost-benefit analysis?

|  |
| --- |
| Cost consequence |

**1.5 Study population**

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| The model cohort is an average risk UK population attending colorectal cancer (CRC) screening.   |  |  |  | | --- | --- | --- | | Input | Proportion | Source | | Proportion of patients with no polyps | 44% | Rastogi et al. | | Proportion of patients with polyps ≤5mm | 38% | Rastogi et al. | | Proportion of patients with polyps >5mm | 18% | Rastogi et al. | | Proportion of polyps that are adenomatous ≤5mm | 17% | Butterly et al. | | Proportion of polyps that are adenomatous >5mm | 10.1 | Butterly et al. | |

**1.6 Institutional setting** Where is/are the intervention(s) being evaluated usually provided?

|  |
| --- |
| Secondary care |

**1.7 Country/ currency**

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

|  |
| --- |
| UK pounds; Costs are from 2014 |

**1.8 Funding source**

|  |
| --- |
| Olympus |

**1.9 Analytical perspective**

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

|  |
| --- |
| English National Health Service and Individual UK hospital perspective |

**2 Effectiveness**

Were the effectiveness data derived from: a single study, a review/ synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  | | --- | --- | --- | | Parameter | Value | Source | | Diminutive polyp optical diagnosis feasibility rate | 75% | Kaltenbach et al. (2014) | | Optical diagnosis sensitivity NBI | 93% | McGill et al.(2013) | | Optical diagnosis specificity NBI | 83% | McGill et al.(2013) | | Probability of hospitalisation for bleeding with polypectomy | 0.43% | Whyte et al. (2011) | | Probability of perforation with polypectomy | 0.28% | Whyte et al. (2011) | |

**3 Intervention Costs**

Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described?

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | INPUT | BASE CASE | SOURCE | | --- | --- | --- | | Unit cost per system NBI | £40,395 | OLYMPUS list price | | Unit cost per scope NBI | £38,660 | OLYMPUS list price | | Training cost per year NBI | £2,272 | OLYMPUS list price | | Maintenance cost NBI system | £3,525 | OLYMPUS list price | | Maintenance cost HD-WLE system | £3,560 | Default value that varies with options selected | | Maintenance cost NBI scopes | £4,805 | OLYMPUS list price | | Maintenance cost HD-WLE scopes | £4,438 | Default value that varies with options selected | | NHS Tariff for colonoscopy - with biopsy | £522 | Monitor 2014 - HRG tariff FZ51Z | | NHS Tariff for colonoscopy - without biopsy | £437 | Monitor 2014 - HRG tariff  FZ52Z | | Cost per histological exam | £110.70 | Calculation | | Cost per Biopsy | £82 | Unpublished data obtained from University College London Hospitals, Plymouth Hospital NHS Trust and South Devon Healthcare NHS Foundation Trust | | Number of biopsies per exam | 1.35 | Assumption based on data reported in Lee et al, 2012 | | Cost per hospital bleed | £318 | Monitor 2014 - HRG tariff FZ38F | | Cost per perforation event | £2,211 | Monitor 2014 - HRG tariff GB01B | | Unit cost per hour for administration & support | £23 | PSSRU 2014 - | | Hours per test for administration & support | 0.30 | Modified from assumptions reported in Sharara et al. 2008 | | Unit cost per hour nurse non-contact time | £41 | PSSRU 2014 - | | Hours per test for nurse non-contact time | 0.42 | Modified from assumptions reported in Sharara et al. 2008 | | Unit cost per hour of consultant time | £142 | PSSRU 2014 | | Hours with consultant, excluding procedure | 0.50 | Modified from assumptions reported in Sharara et al. 2008 | | Length of procedure time in hours with NBI | 0.30 | Bisschops et al. 2012 | | Length of procedure time in hours with comparator | 0.30 | This input varies where options are selected | | Unit cost per hour nurse contact time | £100 | PSSRU 2014 | | Staff and overhead cost NBI | £167.58 | Calculation | | Staff and overhead cost HD-WLE | £167.58 | Calculation | | Snares - cost per pack | £240 | OLYMPUS list price | | Snares - number per pack | 20 | Market data provided by OLYMPUS | | Forceps - cost per pack | £240 | OLYMPUS list price | | Forceps - number per pack | 10 | Market data provided by OLYMPUS | | Cost consumables with resection | 36 | Calculation | |

*indicate the source for individual cost values (if appropriate)*

**3.1 Indirect Costs** (costs due to lost productivity, unpaid inputs to patient care)

Were indirect costs included:

|  |
| --- |
| None |

*indicate the source for individual cost values (if appropriate)*

**4 Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)**

Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described?

|  |
| --- |
| None |

4.1 List the utility values used in the evaluation

|  |
| --- |
| None |

**5 Modelling**

If a model was used, describe the type of model used. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model?

|  |
| --- |
| The model is a cost consequence and budget impact model. The model begins with an at risk cohort of 551,000 people and increases this population by 20% in each of the 7 years of the model. Each successive annual cohort undergoes colonoscopy to detect polyps. Colonoscopy identifies three mutually exclusive patient groups: patients with no polyps, patients with one or more polyps of ≤ 5mm, or patients with one or more polyps >5mm. For NBI, polyps ≤ 5mm are visually diagnosed for adenomas, where there is high confidence that the polyps are hyperplastic the polyps are left in situ, where visual diagnosis has low confidence the polyps are resected and sent for histological examination. All polyps <5mm are resected and histologically examined. For WLE all polyps are resected and sent for histopathology.  The number of true negatives, false negative, true positive and false positive, and the number of histological examination, resects and adverse events for each cohort in each year are calculated. |

5.1 Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

|  |
| --- |
| The model does not include disease progression. |

5.2 What is the model time horizon?

|  |
| --- |
| 7 years |

5.3 What, if any, discount rates have been applied in the model?

|  |
| --- |
| 3.5% per annum for costs and health outcomes |

5.4 If no economic evaluation was conducted, state the manufacturer’s reasons for this.

|  |
| --- |
| Not applicable |

**6 Results/ Analysis**

What measure(s) of benefit were reported in the evaluation?

|  |
| --- |
| True positives correctly identified, histological tests avoided, adverse events avoided |

6.1 Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

|  |
| --- |
| NBI reduced the incidence of colonoscopy-related adverse events by 32% over 7 years. |

6.2 Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

|  |
| --- |
| The cost over 7 years for NBI is £3,112 million and for HD-WLE is £3,253 million, i.e. a saving of £141 million. |

6.3 Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)?

|  |
| --- |
| No, costs and benefits reported separately. |

6.4 Give results of any statistical analysis of the results of the evaluation.

|  |
| --- |
| NA |

6.5 Was any sensitivity analysis performed – if yes, what type(s)?

|  |
| --- |
| Deterministic sensitivity analysis was included in the model, varying the model parameters by +/-10%. |

6.6 What scenarios were tested in the sensitivity analysis?

|  |
| --- |
| None |

6.7 Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

|  |
| --- |
| The sensitivity analysis shows the effect of the parameters on the total difference in costs between NBI and HD-WLE. The cost of colonoscopy and the cost of the histological exams have the greatest impact on model results. |

**7 Conclusions/ Implications**

Give a brief summary of the author’s conclusions from their analysis

|  |
| --- |
| The data presented underscore NBI’s cost effectiveness related to HD-WLE and establish it as a cost effective diagnostic technology for CRC. |

7.1 What are the implications of the evaluation for practice?

|  |
| --- |
| Implementation of NBI potentially leads to a reduction in histopathological tests and adverse events. |

Appendix Parameters and distributions used in the probabilistic sensitivity analysis

| **Parameter** | **Mean value** | **distribution** | **alpha** | **beta** |
| --- | --- | --- | --- | --- |
| NBI Sensitivity | 0.910 | beta | 145.80 | 14.47 |
| NBI Specificity | 0.819 | beta | 167.60 | 37.09 |
| FICE Sensitivity | 0.814 | beta | 91.44 | 20.90 |
| FICE Specificity | 0.850 | beta | 135.14 | 23.82 |
| i-scan Sensitivity | 0.962 | beta | 149.04 | 5.96 |
| i-scan Specificity | 0.906 | beta | 115.09 | 11.91 |
| Proportion Low Confidence Assessments | 0.210 | Fixed |  |  |
| prevalence of adenomas, in patients ≥ 1polyp | 0.698 | beta | 207.39 | 89.6 |
| prevalence 0 adenoma | 0.302 | dirichlet | 89.61 | 207.4 |
| prevalence of low risk patients | 0.535 | dirichlet | 158.98 | 138.0 |
| prevalence of intermediate risk patients | 0.107 | dirichlet | 31.80 | 265.2 |
| prevalence of high risk patients | 0.056 | dirichlet | 16.62 | 280.4 |
| Probability of perforation with polypectomy | 0.003 | beta | 1.38 | 457.23 |
| Probability of perforation death | 0.052 | beta | 4.00 | 73.00 |
| Probability of hospitalisation for bleeding | 0.003 | beta | 1.38 | 457.23 |
| Bleeding adverse event | 0.006 | gamma | 14.20 | 0.0004 |
| Perforation adverse event | 0.010 | gamma | 49.12 | 0.0002 |
| Histopathology colonoscopy (no polypectomy) | £518.36 | gamma | 32.77 | 15.82 |
| Histopathology colonoscopy (polypectomy) | £600.16 | gamma | 36.80 | 16.31 |
| Expected polyps, 0 adenomas | 3.03 | Fixed |  |  |
| Expected polyps, low risk adenomas | 2.00 | Fixed |  |  |
| Expected polyps, intermediate risk adenomas | 4.78 | Fixed |  |  |
| Expected polyps high risk | 8.47 | Fixed |  |  |
| Average adenoma, LR patients | 1.40 | Fixed |  |  |
| Average adenoma, IR patients | 3.34 | Fixed |  |  |
| Average adenoma, HR patients | 5.91 | Fixed |  |  |
| Cost of treating bowel perforation | £2,152.77 | gamma | 11.38 | 189.10 |
| Cost of admittance for bleeding | £475.54 | gamma | 39.74 | 11.97 |
| Pathology cost | £28.82 | gamma | 6.57 | 4.39 |
| Training cost, per endoscopy | £14.72 | gamma | 42.68 | 0.34 |

Appendix Derivation of the distribution of adenomas in patients undergoing colonoscopy

We searched for studies that described the distribution of polyps in patients in a screening population. We identified one study by Raju and colleagues who reported data for the distribution of polyps and adenomas per patient. We analysed the distribution of polyps and adenomas to derive the average number of polyps and adenomas for low risk (LR), intermediate risk (IR) and high risk (HR) patients and the frequency of patients in each risk category, assuming all polyps are diminutive.

We used a graphical data extraction programme (XY Scan) to extract the data from Raju and colleagues. This extraction resulted in a slight overestimation of the number of adenomas,(426 instead of the reported 422) and the number of patients with adenomas (207 instead of 206) in order to keep polyp numbers correct at 882.

The distribution of polyps for patients with one or more polyp is shown in Table 69 and the distribution adenomas for patients with more than one polyp is shown in Table 70. As seen in Table 70, the proportion of patients with one or more polyps and who have no adenomas is 30.2%.

Table Distribution of polyps in patients with more than one polyp in Raju et al.

|  |  |  |
| --- | --- | --- |
| 1 or more polyps | |  |
| # | % | People |
| 1 | 26.45% | 79 |
| 2 | 25.58% | 76 |
| 3 | 18.60% | 55 |
| 4 | 11.92% | 35 |
| 5 | 7.56% | 22 |
| 6 | 4.07% | 12 |
| 7 | 2.62% | 8 |
| 8 | 1.16% | 3 |
| 9 | 0.87% | 3 |
| 10 | 0.29% | 1 |
| 11 | 0.87% | 3 |
| Total | 100.00% | 297 |

Table Distribution of adenomas in patients with one or more polyp in Raju et al.

|  |  |  |  |
| --- | --- | --- | --- |
| Adenomas | | People | Adenomas |
| # | % |
| 0 | 0.302 | 90 | 0 |
| 1 | 0.324 | 96 | 96 |
| 2 | 0.212 | 63 | 126 |
| 3 | 0.071 | 21 | 63 |
| 4 | 0.036 | 11 | 43 |
| 5 | 0.036 | 11 | 54 |
| 6 | 0.007 | 2 | 13 |
| 7 | 0.002 | 1 | 5 |
| 8 | 0.000 | 0 | 0 |
| 9 | 0.010 | 3 | 26 |
| 10 | 0.000 | 0 | 0 |
| 11 | 0.000 | 0 | 0 |
| Total | 1.0000 | 297 | 426 |

In order to calculate the number of polyps per patient in each risk category, we assumed that the overall prevalence of patients with adenomas was evenly distributed across the risk categories, where people had adenomas. The risk stratification was defined according to the current BSG guidelines where people with 1-2 adenomas are low risk, those with 3-4 adenomas are intermediate risk and those with five or more adenomas are high risk. The proportion of patients in each risk category is shown in Table 71. The expected number of adenomas in each risk category is calculated as a weighted average. The expected number of polyps for each risk category is calculated by assuming a constant prevalence of 0.68 adenomas per polyp in each risk category.

Table Proportion of patients and expected number of adenoma in each risk category

|  |  |  |  |
| --- | --- | --- | --- |
|  | Proportion of patients | Expected number of adenoma | Expected number of polyps |
| Low risk (0-2 adenoma) | 0.837 | 1.40 | 2.00 |
| Intermediate risk (3-4 adenoma) | 0.107 | 3.34 | 4.78 |
| High risk (5+ adenoma) | 0.056 | 5.91 | 8.47 |

Appendix System costs (scope, system, maintenance)

The equipment and maintenance costs for virtual chromoendoscopy technologies have been supplied by the manufacturers of the systems are shown in Table 72. These costs are not included in the base case analysis for virtual chromoendoscopy versus histopathology as all equipment and maintenance costs are included within the National Reference Costs for colonoscopy and polypectomy.

Table Equipment and maintenance costs for virtual chromoendoscopy technologies

|  |  |  |  |
| --- | --- | --- | --- |
| **Item** | NBI | FICE | i-scan |
| Processor / light source cost | £40,395.00 | £28,500.00 | £48,760.00 |
| Scope cost | £38,660.00 | £25,712.50 | £30,700.00 |
| Scope maintenance per year | £4,805.00 | £2,900.00 | £2,314.29 |
| System maintenance per year | £3,525.00 | £2,200.00 | £1,842.86 |

The costs of the virtual chromoendoscopy systems and scope were calculated assuming that systems lasted for 7 years and an equivalent discount rate of 3% per annum.

Assuming that payment is made in advance on the annuitisation, a useful life (n) of 7 years for a system and scope, and assuming that the discount rate (r) in NICE appraisals (3.5%) represents social time preference, the annuity factor can be calculated using the following equation:

Assuming annuitized costs, the annual cost of the system and scope per year is

, where the annualisation factor =

= 6.329 years.

The costs of the systems and scopes are calculated per endoscopy performed by dividing the cost per year by the number of endoscopies performed per system or scope. We used the Solon and colleagues estimates for the number of scopes and systems per year. They estimated there would be 1071 systems and 5 scopes per system. We used the total number of colonoscopies from the national reference costs (302,422 per year).

Within the model, the average cost per year is calculated for virtual chromoendoscopy technologies by calculating the weighted average by market share, with an estimated market share, according to the companies’ submissions (NBI 74%, FICE 13%, i-scan 13%).

We calculated the cost for the virtual chromoendoscopy technologies per endoscopy to be £228.74.

The cost for the virtual chromoendoscopy technologies are shown in Table 73.

Table Equipment and maintenance costs per endoscopy performed for virtual chromoendoscopy technologies

|  |  |  |
| --- | --- | --- |
| Virtual chromoendoscopy technique | Total cost per endoscopy | Difference compared to average cost |
| NBI | £232.85 | £20.55 |
| FICE | £146.99 | -£65.31 |
| i-scan | £160.64 | -£51.66 |

Appendix Colorectal cancer clinical outcomes from the SBCS model

The ScHARR SBCS model provided estimates of colorectal cancer incidence for patients in each of the categories in the EAG model, i.e. by whether patients had all adenomas resected and what surveillance interval they were assigned to. These estimates ranged from 1.1% to 4.2% as shown in the table below. We then calculated the incidence of colorectal cancer for the total population by multiplying these estimates by the proportion in each group. The calculated incidence of lifetime risk of colorectal cancer is 3.025% for those receiving histopathology, 3.020% for those receiving NBI, 3.045% for those receiving FICE and 3.021% for those receiving i-scan.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Underlying Health state at colonoscopy | Status post polypectomy | Follow up received | CRC deaths | CRC Incidence |
| Normal epithelium | NA | invited to screening | 0.00575 | 0.01131 |
| LR adenomas | all adenomas resected | invited to screening | 0.02145 | 0.04215 |
| HR adenomas (IR) | all adenomas resected | invited to screening | 0.02141 | 0.04207 |
| HR adenomas (HR) | all adenomas resected | invited to screening | 0.02140 | 0.04205 |
| LR adenomas OR HR adenomas | LR adenomas remain postpolypectomy | invited to screening | 0.02132 | 0.04187 |
| LR adenomas OR HR adenomas | HR adenomas remain post polypectomy | invited to screening | 0.20775 | 0.43476 |
| Normal epithelium | NA | 3-yearly surveillance | 0.00460 | 0.00955 |
| LR adenomas | all adenomas resected | 3-yearly surveillance | 0.01240 | 0.02689 |
| HR adenomas (IR) | all adenomas resected | 3-yearly surveillance | 0.01238 | 0.02685 |
| HR adenomas (HR) | all adenomas resected | 3-yearly surveillance | 0.01238 | 0.02684 |
| LR adenomas OR HR adenomas | LR adenomas remain postpolypectomy | 3-yearly surveillance | 0.01238 | 0.02677 |
| LR adenomas OR HR adenomas | HR adenomas remain post polypectomy | 3-yearly surveillance | 0.02533 | 0.13572 |
| Normal epithelium | NA | annual surveillance | 0.00435 | 0.00913 |
| LR adenomas | all adenomas resected | annual surveillance | 0.01123 | 0.02518 |
| HR adenomas (IR) | all adenomas resected | annual surveillance | 0.01122 | 0.02514 |
| HR adenomas (HR) | all adenomas resected | annual surveillance | 0.01121 | 0.02513 |
| LR adenomas OR HR adenomas | LR adenomas remain postpolypectomy | annual surveillance | 0.01122 | 0.02513 |
| LR adenomas OR HR adenomas | HR adenomas remain post polypectomy | annual surveillance | 0.01193 | 0.03684 |