National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Virtual chromoendoscopy for real-time assessment of colorectal polyps during colonoscopy

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read in conjunction with the final scope issued by NICE for the assessment and the diagnostics assessment report. A glossary of terms can be found in Appendix B.

1 Background

1.1 Introduction

The purpose of this assessment is to evaluate the clinical and cost effectiveness of virtual chromoendoscopy (Narrow Band Imaging [NBI], Flexible Spectral Imaging Colour Enhancement [FICE] and i-scan) for real-time assessment of diminutive (5 mm or less) colorectal polyps.

Colorectal polyps, that is, fleshy growths on the lining of the colon, may be found during a colonoscopy. Polyps are not usually cancerous; but some (known as adenomatous polyps) will eventually turn into cancer if left untreated. In current clinical practice, all detected colon polyps (except some in the rectosigmoid area) are removed and their histopathology is examined to determine whether they are adenomatous, and therefore at high risk of

cancer, or hyperplastic, and so at low risk. Conventional white light endoscopy is currently used to detect polyps, and may be used in combination with dyes (chromoendoscopy) to make it easier to see the surface pattern and blood vessels in the colon. Virtual chromoendoscopy technologies aim to allow colour-enhanced visualisation of blood vessels and surface pattern compared with conventional endoscopy, but without using dyes. This may allow real-time differentiation of adenomas and hyperplastic colorectal polyps during colonoscopy, which could lead to the fewer resections of low-risk hyperplastic polyps (with a resulting reduction in complications); quicker results and management decisions; and reduced resource use through fewer histopathology examinations.

The DISCARD (Detect, InSpect, ChAracterize, Resect, and Discard) strategy is an approach that aims to allow endoscopists to assess the histopathology of diminutive and small polyps (9 mm or less) during colonoscopy (Ignjatovic et al. 2009). Small or diminutive polyps confidently identified as adenomatous can be removed and discarded, that is, not sent for histological examination. Small and diminutive polyps in the rectosigmoid area confidently identified (high confidence) as hyperplastic polyps can be left in place. However, all small or diminutive polyps that the endoscopist cannot make a confident assessment of (low confidence) should be removed and sent for histological examination. The DISCARD strategy is not currently used in clinical practice in the NHS; but, in some centres diminutive polyps in the rectosigmoid area are optically diagnosed using white light or virtual chromoendoscopy and left in place if there is high confidence the polyps are hyperplastic.

The preservation and incorporation of valuable endoscopic innovations (PIVI) initiative is a programme from the American Society for Gastrointestinal Endoscopy (ASGE), which outlines the criteria that an endoscopic technology must meet before being considered appropriate for use in US clinical practice.

The criteria on the real-time endoscopic assessment of diminutive colorectal polyps are as follows:

- For colorectal polyps 5 mm or less in size to be removed and discarded without pathologic assessment, the endoscopic technology used should have a 90% or more agreement in the assignment of post-polypectomy surveillance intervals compared with decisions based on pathology assessment of all identified polyps.
- For a technology to be used to guide the decision to leave suspected rectosigmoid hyperplastic polyps 5 mm or less in place, the technology should have a negative predictive value of more than 90% for adenomatous polyp histology.

Provisional recommendations on using virtual chromoendoscopy technologies for real-time assessment of diminutive colorectal polyps will be formulated by the diagnostics advisory committee at the committee meeting on 23 November 2016.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	Does virtual chromoendoscopy for real-time assessment of diminutive (1 to 5 mm) colorectal polyps during colonoscopy represent a cost-effective use of NHS resources?
Populations	• 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 referred for colonoscopy through the NHS bowel cancer screening programme
Interventions	• Narrow Band Imaging (Olympus Medical Systems) • FICE (Fujinon/Aquilant Endoscopy) • i-scan (Pentax Medical) (Used with high definition or high resolution monitors and endoscopes without the use of magnification) The following factors should also be considered in addition to the different interventions: • level of expertise and experience in optical assessment of polyps • level of confidence in polyp assessment • location of polyp • use of different classification criteria
Comparator	Histopathology
Healthcare setting	Secondary and tertiary care
Outcomes	Intermediate measures for consideration may include: • Accuracy of assessment of polyp histopathology • Number of polyps left in place • Number of polyps removed and discarded • Number of polyps removed and sent for histological examination • Recommended surveillance interval • Length of time to perform the colonoscopy • Number of outpatient appointments/telephone consultations
	Patient-reported outcomes for consideration may include: • Health related quality of life including anxiety

	Clinical outcomes for consideration may include: • Adverse effects of polypectomy • Colorectal cancer • Mortality
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Endoscopy system costs • Colonoscopy and related outpatient appointments/telephone consultations • Training • Histopathology • Colorectal cancer treatment • Treatment of adverse effects of polypectomy
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

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

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG). In the context of this guidance, the definitions of the terms used to describe diagnostic accuracy are as follows:

- Sensitivity is the ability of the test to correctly identify diminutive polyps as adenomas.
- Specificity is the ability of the test to correctly identify diminutive polyps as hyperplastic polyps.
- Negative predictive value is the probability that people with a negative test result do not have an adenoma.

2.1 Clinical effectiveness

The EAG did a systematic review of the evidence on the clinical effectiveness of virtual chromoendoscopy (Narrow Band Imaging [NBI], Flexible Spectral Imaging Colour Enhancement [FICE] and i-scan).

In total, 30 studies were included in the review. Studies were included if they assessed the use of virtual chromoendoscopy compared with a histopathology assessment of resected diminutive colorectal polyps. Included studies also reported on at least 1 of the outcomes and populations listed in the scope (table 1). All included studies were appraised using the QUADAS checklist.

Studies were excluded if:

- Real-time diagnosis was not used, that is, diagnosis was not made during the colonoscopy.
- Only endoscopes with a push-button 'near focus' capability were used, because these endoscopes use magnification; unless it was clear that the 'near focus' function had not been used during polyp characterisation.
- The population was being monitored for irritable bowel syndrome, polyposis syndrome, or familial adenomatous polyposis.

Further details of the systematic review inclusion criteria can be found starting on page 41 of the diagnostic assessment report.

There were 22 studies on NBI, 4 studies on i-scan and 2 studies on FICE. Two studies also included more than 1 technology (1 study on NBI and FICE; and 1 study on NBI and i-scan). Fourteen studies were done in the US, 11 in Europe, of which 4 were in the UK, 4 in Asia and 1 in Australia. Most studies were carried out in specialist centres.

As part of the review, bivariate meta-analyses were done for all of the technologies (NBI, FICE and i-scan) to calculate summary values for the sensitivity and specificity of the tests. A summary table of the bivariate meta-

analyses results can be seen in table 24 starting on page 124 of the diagnostics assessment report.

None of the included studies reported on health-related quality of life, mortality, incidence of colorectal cancer, or number of outpatient appointments.

Virtual chromoendoscopy using Narrow Band Imaging

Study characteristics and critical appraisal

Twenty-four studies included in the systematic review reported on the use of NBI. Most were done in a single centre and the results might not be generalisable to other centres. Fourteen of these studies were carried out in the US, 5 in Europe, 4 in Asia and 1 in Australia. Seven reported on diminutive polyps, 9 on small polyps and 8 on polyps of any size.

The endoscopists' levels of experience of using NBI varied: all of them had experience in 8 studies, some had experience in 4 studies, none had experience in 4 studies, and the experience levels were unclear for 8 studies. Table 5 starting on page 53 of the diagnostic assessment report contains a detailed overview on the studies that were included.

Three studies reported on adverse events, all of which stated that no complications were experienced as a result of the test.

None of the studies reported on colorectal cancer, mortality, health-related quality of life, or the number of outpatient appointments or telephone consultations.

The QUADAS assessment of the studies found that all of them were at low risk of bias. It was unclear whether 4 of the studies were at risk of spectrum bias, because the reason for patients having a colonoscopy was not reported.

The full results of the QUADAS assessment can be found in table 6 on page 60 of the diagnostic assessment report.

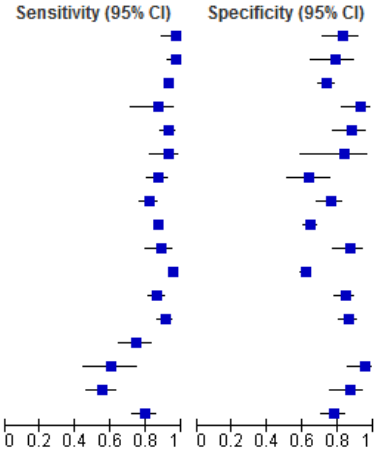
Accuracy of Narrow Band Imaging for characterising diminutive colorectal polyps in any part of the colon

Seventeen studies reported the sensitivity of NBI and 16 studies reported on the specificity of NBI for characterisations of polyps made with any level of confidence. The sensitivity of NBI reported in the studies ranged from 0.55 to 0.97 and the specificity ranged from 0.62 to 0.95 (Figure 1).

Bivariate meta-analysis of the 16 studies reporting on both sensitivity and specificity produced summary values of 0.88 (95% confidence interval [CI] 0.83 to 0.92) for sensitivity and 0.81 (95% CI 0.75 to 0.85) for specificity.

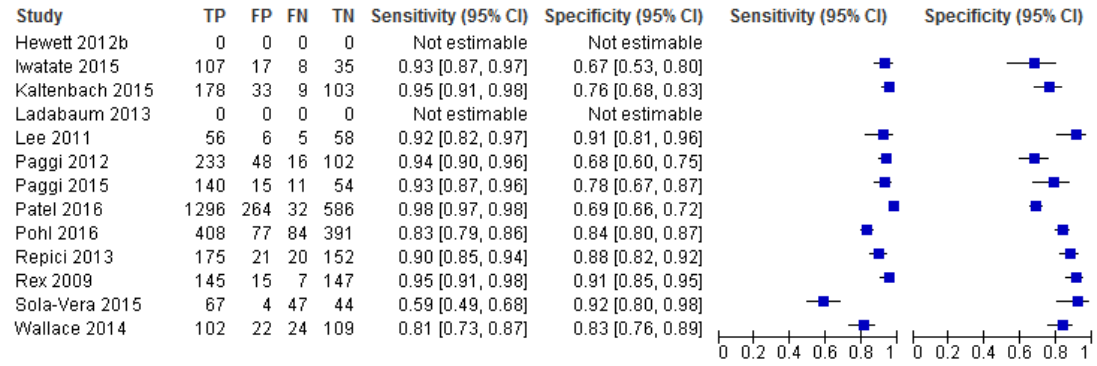
Figure 1 Accuracy of NBI for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Aihara 2016	60	10	2	49	0.97 [0.89, 1.00]	0.83 [0.71, 0.92]
Chandran 2015	105	11	3	40	0.97 [0.92, 0.99]	0.78 [0.65, 0.89]
Gupta 2012	484	97	37	266	0.93 [0.90, 0.95]	0.73 [0.68, 0.78]
Henry 2010	32	4	5	49	0.86 [0.71, 0.95]	0.92 [0.82, 0.98]
Ignjatovic 2009	144	7	11	51	0.93 [0.88, 0.96]	0.88 [0.77, 0.95]
Ikematsu 2015	50	3	4	15	0.93 [0.82, 0.98]	0.83 [0.59, 0.96]
Iwatate 2015	123	25	18	44	0.87 [0.81, 0.92]	0.64 [0.51, 0.75]
Kang 2015	190	37	42	115	0.82 [0.76, 0.87]	0.76 [0.68, 0.82]
Ladabaum 2013	995	252	155	456	0.87 [0.84, 0.88]	0.64 [0.61, 0.68]
Lee 2011	71	10	9	66	0.89 [0.80, 0.95]	0.87 [0.77, 0.94]
Patel 2016	1523	490	77	786	0.95 [0.94, 0.96]	0.62 [0.59, 0.64]
Repici 2013	203	31	32	163	0.86 [0.81, 0.90]	0.84 [0.78, 0.89]
Rex 2009	178	28	17	172	0.91 [0.86, 0.95]	0.86 [0.80, 0.90]
Rogart 2008	71	0	24	0	0.75 [0.65, 0.83]	Not estimable
Shahid 2011	27	3	18	55	0.60 [0.44, 0.74]	0.95 [0.86, 0.99]
Sola-Vera 2015	85	8	70	53	0.55 [0.47, 0.63]	0.87 [0.76, 0.94]
Wallace 2014	120	35	31	124	0.79 [0.72, 0.86]	0.78 [0.71, 0.84]



Eleven studies reported on the sensitivity and specificity of NBI for assessing polyps that were characterised with high confidence (Figure 2). Bivariate meta-analysis produced summary values of 0.91 (95% CI 0.85 to 0.95) for sensitivity and 0.82 (95% CI 0.76 to 0.87) for specificity.

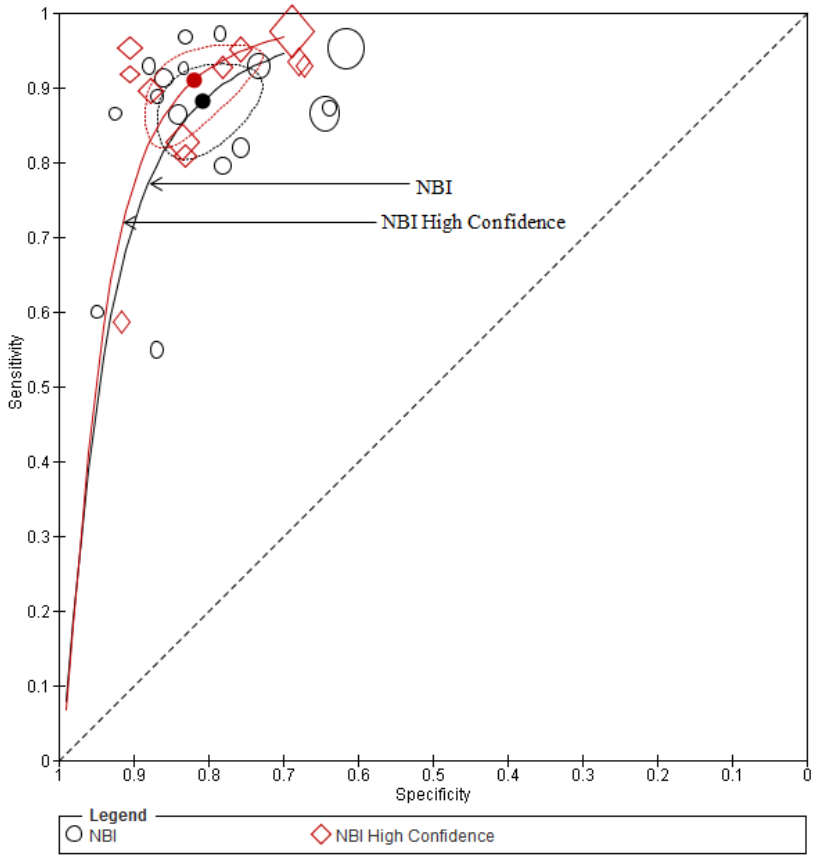
Figure 2 Accuracy of NBI high confidence decisions for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps in the whole colon.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hewett 2012b	0	0	0	0	Not estimable	Not estimable
Iwatate 2015	107	17	8	35	0.93 [0.87, 0.97]	0.67 [0.53, 0.80]
Kaltenbach 2015	178	33	9	103	0.95 [0.91, 0.98]	0.76 [0.68, 0.83]
Ladabaum 2013	0	0	0	0	Not estimable	Not estimable
Lee 2011	56	6	5	58	0.92 [0.82, 0.97]	0.91 [0.81, 0.96]
Paggi 2012	233	48	16	102	0.94 [0.90, 0.96]	0.68 [0.60, 0.75]
Paggi 2015	140	15	11	54	0.93 [0.87, 0.96]	0.78 [0.67, 0.87]
Patel 2016	1296	264	32	586	0.98 [0.97, 0.98]	0.69 [0.66, 0.72]
Pohl 2016	408	77	84	391	0.83 [0.79, 0.86]	0.84 [0.80, 0.87]
Repici 2013	175	21	20	152	0.90 [0.85, 0.94]	0.88 [0.82, 0.92]
Rex 2009	145	15	7	147	0.95 [0.91, 0.98]	0.91 [0.85, 0.95]
Sola-Vera 2015	67	4	47	44	0.59 [0.49, 0.68]	0.92 [0.80, 0.98]
Wallace 2014	102	22	24	109	0.81 [0.73, 0.87]	0.83 [0.76, 0.89]

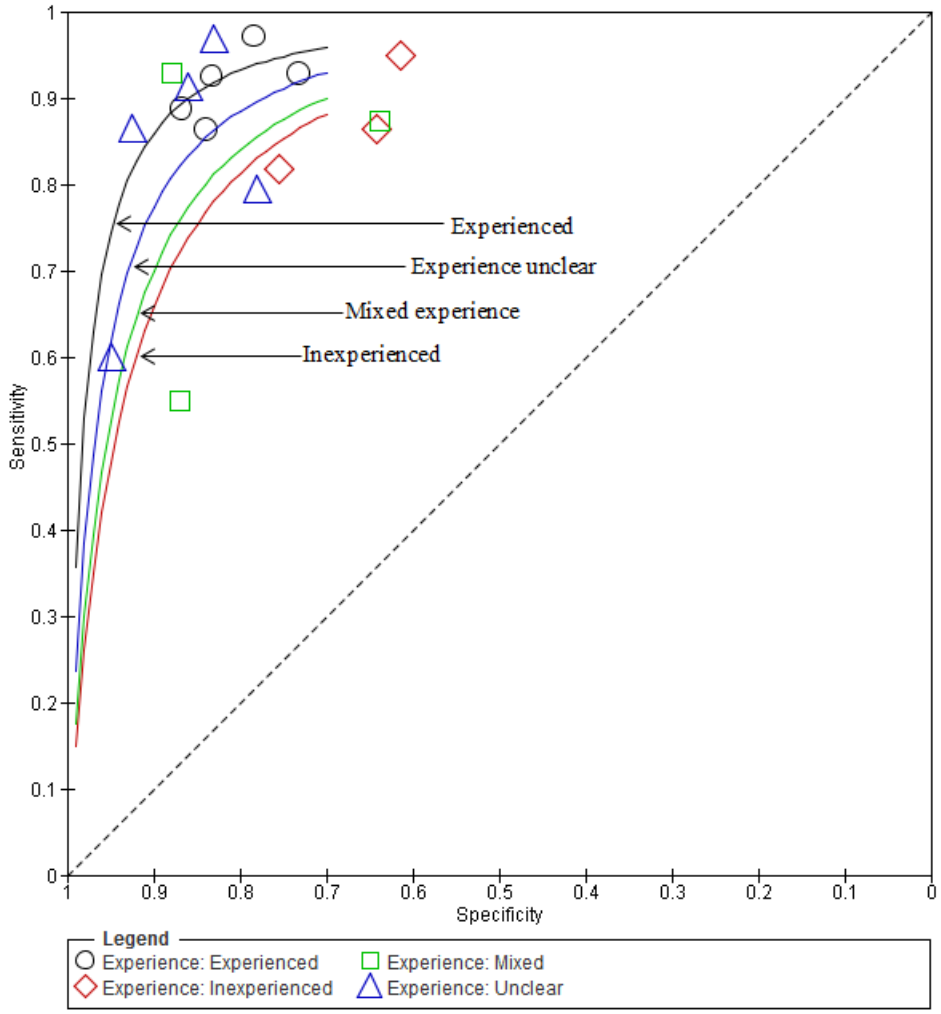
The bivariate meta-analysis found that the sensitivity and specificity of NBI was higher for polyps diagnosed with high confidence, compared with those diagnosed with any level of confidence (that is those assessed with low and high confidence; Figure 3).

Figure 3 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.



The effect of the experience of the endoscopist on the sensitivity and specificity of NBI was investigated and the results can be seen in Figure 4. Only a small number of studies reported on the level of experience of the endoscopist, so the results should be interpreted with caution.

Figure 4 Figure 6 SROC plots for all characterisations of polyps in the whole colon by endoscopist level of experience using NBI.



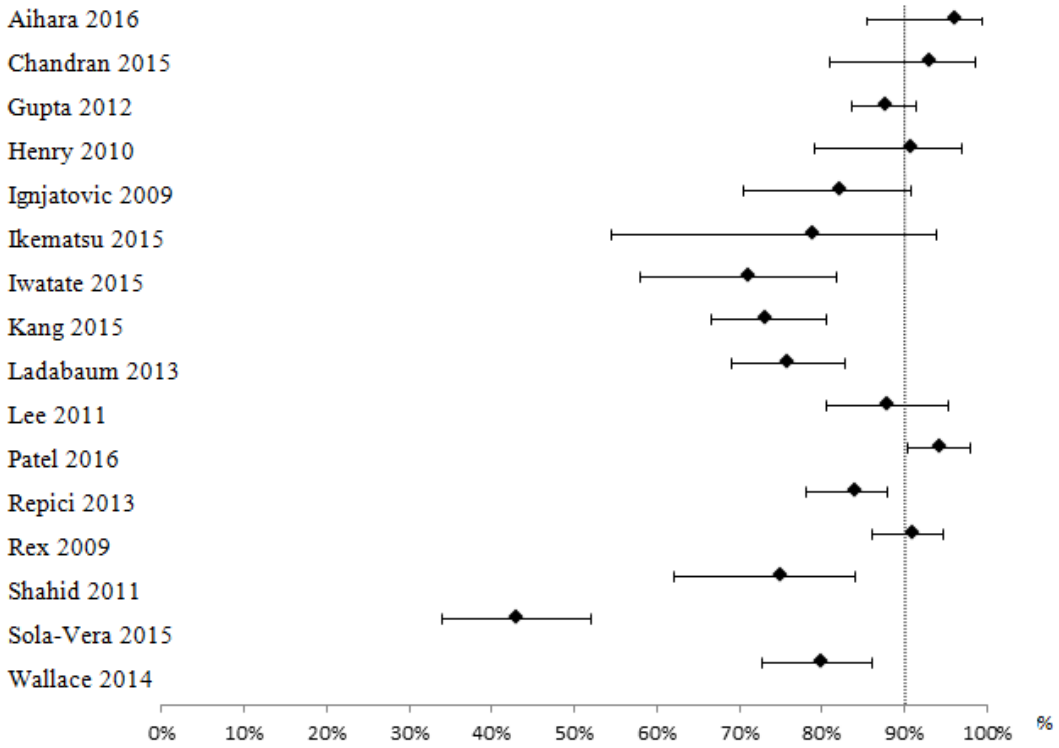
A post-hoc bivariate meta-analysis was run which only included studies with endoscopists who were experienced in using NBI (4 studies). The analysis produced summary values of 0.92 (95% CI 0.89 to 0.94) for sensitivity and 0.82 (95% CI 0.72 to 0.89) for specificity. Compared with the bivariate analysis for endoscopists with different levels of experience, the point

estimate for sensitivity increased slightly from 0.91 to 0.92 and the specificity did not change. The confidence interval for sensitivity narrowed from (0.85 to 0.95) for endoscopists with a variety of experience to (0.89 to 0.94) for experienced endoscopists. The confidence interval for specificity for experienced endoscopists (0.76 to 0.87) widened compared with endoscopists with different levels of experience (0.72 to 0.89).

Negative predictive value of Narrow Band Imaging for characterising polyps in any part of the colon

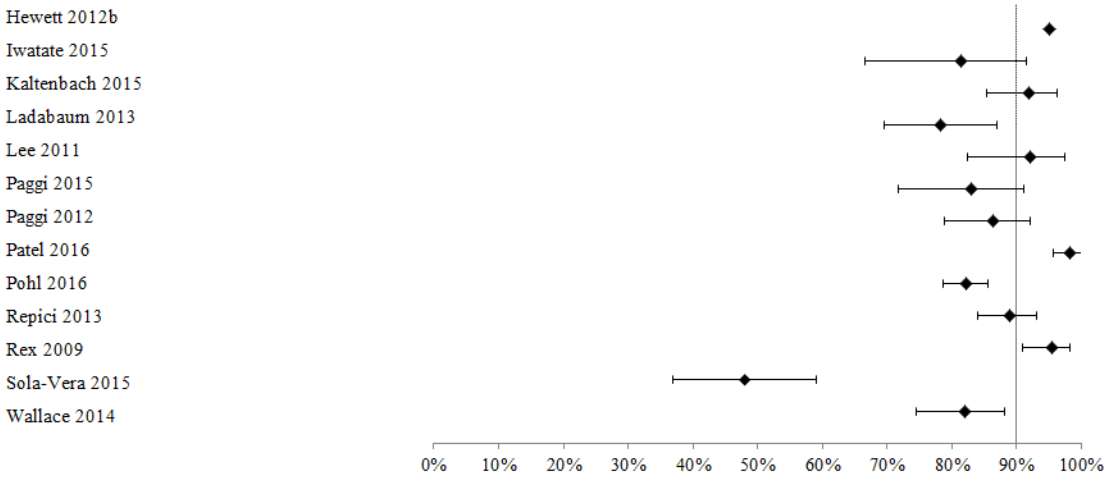
Sixteen studies reported on the negative predictive value of NBI for characterising diminutive polyps in the whole colon, made with any level of confidence. The negative predictive value ranged from 43% to 96%. The lower bound of the 95% confidence interval fell below 90% in all studies apart from Patel et al. (2016). A forest plot showing the study results can be seen in Figure 5.

Figure 5 NPV of NBI for all characterisations of diminutive polyps in the whole colon (made with any level of confidence)



Thirteen studies reported on the negative predictive value for high confidence characterisations of polyps. The negative predictive value was higher for characterisations made with high confidence compared with those made with all levels of confidence. The range was 48% to 98%. When reported, the lower bound of the 95% confidence interval fell below 90% in all but 2 studies (Patel et al. 2016; Rex 2009). A forest plot showing the study results can be seen in Figure 6.

Figure 6 NPV of NBI for high confidence characterisations of diminutive polyps in the whole colon



Note: Hewett 2012b did not report 95% confidence intervals

One study looked at the difference between the negative predictive value of characterisations done by specialists in colonoscopy and general endoscopists (Iwatate et al. 2015). The study found that specialists achieved a higher negative predictive value (90.9%; CI 70.8 to 98.9]) than generalists (71.4%; 95% CI 47.8 to 88.8). However, the difference was not statistically significant.

Further details of the negative predictive value results can be found in table 14 starting on page 93 of the diagnostic assessment report.

Accuracy of Narrow Band Imaging for characterising polyps in the rectosigmoid colon

Four studies reported on the sensitivity and specificity of NBI for assessing polyps in the rectosigmoid colon. Bivariate meta-analysis including 3 of these studies was possible, which produced summary values of 0.85 (95% CI 0.75 to 0.91) for sensitivity and 0.87 (95% CI 0.74 to 0.94) for specificity.

A post-hoc bivariate meta-analysis was run for the 2 studies that included endoscopists who were experienced in using NBI. It produced summary values of 0.90 (95% CI 0.71 to 0.97) for sensitivity and 0.98 (95% CI 0.91 to 1.00) for specificity. When compared with the bivariate analysis for endoscopists with different levels of experience, the point estimate for sensitivity increased from 0.87 to 0.90 and the point estimate for specificity increased from 0.95 to 0.98. The confidence interval for sensitivity for endoscopists with a variety of experience (0.80 to 0.92) widened compared with experienced endoscopists (0.71 to 0.97). The confidence interval for specificity for experienced endoscopists (0.87 to 0.98) narrowed compared with endoscopists (0.91 to 1.00) with mixed levels of experience.

Other outcomes

One study reported on the number of polyps that would have been left in place during NBI assessment, if the strategy was to leave diminutive hyperplastic polyps in the rectosigmoid colon (Ignatovic et al. 2009). The endoscopists in the study identified 33 polyps that would have been left in place, out of a total of 323 small and diminutive polyps that were assessed with high confidence.

Two studies reported on the number of diminutive polyps that would have been resected and discarded, if a discard type strategy was used. Gupta et al. (2012) reported that 884 out of 1254 (70.5%) diminutive polyps in the study would have been resected and discarded. Ignatovic et al. (2009) reported that

290 out of 323 small and diminutive polyps assessed with high confidence diagnosis would have been resected and discarded.

One study reported on the number of diminutive polyps identified for resection and histopathological examination. Ignatovic et al. (2009) reported that 22 out of 293 polyps assessed with low confidence would have been sent to histopathology.

Thirteen studies reported on the agreement between surveillance intervals set when using NBI compared with those set by histopathology; agreement ranged from 84% to 99%.

Virtual chromoendoscopy using i-scan

Study characteristics and critical appraisal

Five studies included in the systematic review reported on the use of i-scan. The EAG noted that most of the studies were done in a specialist endoscopy centre by 1 endoscopist. So, it is unclear how generalisable the results are to different settings. The EAG also noted that the populations in most of the studies are likely to be representative of people who have colonoscopy in the UK, except for the study by Hoffman et al. (2010) because it did not give sufficient details about the participants.

Four studies were done in Europe and 1 in Asia. The only meta-analysis possible was for high confidence characterisations of diminutive polyps in the whole colon.

One study, reporting on adverse events (Lee et al. 2011), stated that participants did not have any procedure-related complications.

Three studies reported that the endoscopists had experience of using i-scan. The remaining 2 studies did not report on this (Pigo et al. 2013; Rath et al. 2015).

Further details on the characteristics of the included studies can be found on page 64 in table 7 of the diagnostic assessment report.

The QUADAS assessment found that all of the studies were at low risk of bias. The full results of the QUADAS assessment can be found in table 8 on page 66 of the diagnostics assessment report.

Accuracy of i-scan for characterising colorectal polyps in the whole colon

Two studies reported on high confidence characterisations of polyps in the whole colon (Basford et al. 2014; Lee et al. 2011). Bivariate meta-analysis produced summary values of 0.96 (95% CI 0.92 to 0.98) for sensitivity and 0.91 (95% CI 0.84 to 0.95) for specificity.

Two studies reported that the negative predictive value of i-scan for detecting colorectal polyps in the whole colon was above 90% (Lee et al. 2011, Hoffman et al. 2010). But, the lower bound of the confidence interval for both studies was below 90%. Full results can be seen in table 17 on page 104 of the diagnostic assessment report.

Accuracy of i-scan for characterising polyps in the distal or rectosigmoid colon

Two studies reported that the negative predictive value of i-scan for detecting colorectal polyps in the distal or rectosigmoid colon was above 90% (Rath et al. 2005; Pigo et al. 2013). But, the lower bounds of the confidence interval were below 90%.

Virtual chromoendoscopy using Flexible Spectral Imaging Colour Enhancement

Study characteristics and critical appraisal

Three studies in the systematic review reported on the use of FICE. Two studies were done in the UK (Longcroft-Wheaton et al. 2011; 2012) and 1

study was done in South Korea (Kang et al. 2015). All studies were carried out in single centres and none reported on any criteria associated with the preservation and incorporation of valuable endoscopic innovation (PIVI) initiative. Also, none reported on high confidence characterisations of diminutive polyps or on a specific part of the colon.

One study reported that the endoscopists did not have any experience of using Flexible Spectral Imaging Colour Enhancement (FICE; Kang et al. 2015). In the remaining 2 studies it was unclear whether the endoscopists had any experience (Longcroft-Wheaton et al. 2011 and 2012).

Further details on the characteristics of the included studies can be found in the diagnostic assessment report in table 9 starting on page 69.

Accuracy of Flexible Spectral Imaging Colour Enhancement for characterising diminutive colorectal polyps in any part of the colon

All 3 studies reported the sensitivity and specificity of FICE for characterising polyps in any part of the colon. The sensitivity of FICE reported in the studies ranged from 0.74 to 0.88 and the specificity ranged from 0.82 to 0.88 (**Error! eference source not found.**). Bivariate meta-analysis using all 3 studies produced summary values of 0.81 (95% CI 0.73 to 0.88) for sensitivity and 0.85 (95% CI 0.79 to 0.90) for specificity. The negative predictive value ranged from 70% to 84%; full results can be seen in Table 2.

Figure 7 Accuracy of FICE for characterising diminutive colorectal polyps as either adenomas or hyperplastic polyps

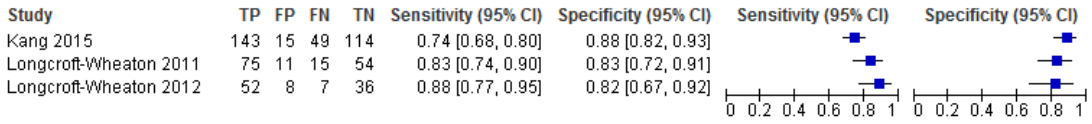


Table 2 Negative predictive value of Flexible Spectral Imaging Colour Enhancement for characterising diminutive colorectal polyps

Study	Value	95% CI
Kang et al. 2015	70%	63% to 77%
Longcroft-Wheaton et al. 2011	78%	70% to 84%
Longcroft-Wheaton et al. 2012	84%[a]	69% to 93%[a]
[a] Value calculated by the reviewer		
Abbreviation: CI, confidence interval.		

2.2 Costs and cost effectiveness

The EAG carried out a search to identify studies that investigated the cost effectiveness of virtual chromoendoscopy. The EAG also constructed a de novo economic model to assess the cost effectiveness of virtual chromoendoscopy (NBI, i-scan and FICE) compared with histopathology.

Systematic review of cost-effectiveness evidence

The EAG did a systematic review to identify any full economic evaluations comparing virtual chromoendoscopy with histopathology and including long-term outcomes such as quality-adjusted life years (QALYs), length of survival or incidence of colorectal cancer. Two studies met the inclusion criteria (Hassan et al. 2010; Kessler et al. 2011). The EAG critically appraised the studies using a checklist based on the Drummond checklist (table 26 on page 130 of the diagnostic assessment report) and noted that both studies clearly reported their parameters, assumptions and methods. The EAG noted that it is unclear how generalisable the results are to the UK NHS, because they used non-UK resource costs and did not assess health outcomes using QALYs.

The cost effectiveness for both studies was reported as the cost per life year gained. Hassan et al. found no difference in life expectancy between the 2 strategies and therefore could not calculate a cost per life year gained.

Kessler et al. found that the cost per life year gained for the submit-all strategy, that is sending all polyps detected during colonoscopy for histological analysis, compared with a resect and discard strategy was US$377,460.

Economic analysis

The EAG developed a de novo economic model to assess the cost effectiveness of virtual chromoendoscopy (NBI, i-scan and FICE) compared with histopathology for assessing colorectal polyps.

Model structure

The model is a decision tree; a simplified diagram of the model structure can be seen in **Error! Reference source not found.**. The decision tree estimates he short-term costs and outcomes of the first colonoscopy. People enter the model having had at least 1 diminutive polyp and no non-diminutive polyps identified. In the model, polyps are assessed and a surveillance interval is assigned. A second existing model was used in addition to the decision tree to estimate the long-term costs and QALYs for each surveillance classification, including incorrect surveillance classifications. The second model is a state transition model developed by the School of Health and Related Research (ScHARR), at the University of Sheffield, for the national bowel cancer screening programme. The model was chosen because it is a long-standing model that has been validated and was used to inform the introduction of the screening programme. The model was run independently and the cost and QALY estimates were entered as parameters at the endpoints of the decision tree model.

<u>The decision tree model</u>

The decision tree compares the virtual chromoendoscopy strategies with a histopathology strategy. It has 4 main arms, 1 for each test that was assessed; NBI, i-scan, FICE and standard endoscopy with histopathology. In

Error! Reference source not found., arm A of the decision tree represents he structure used for the index tests (NBI, i-scan and FICE) and arm B is the comparator (histopathology).

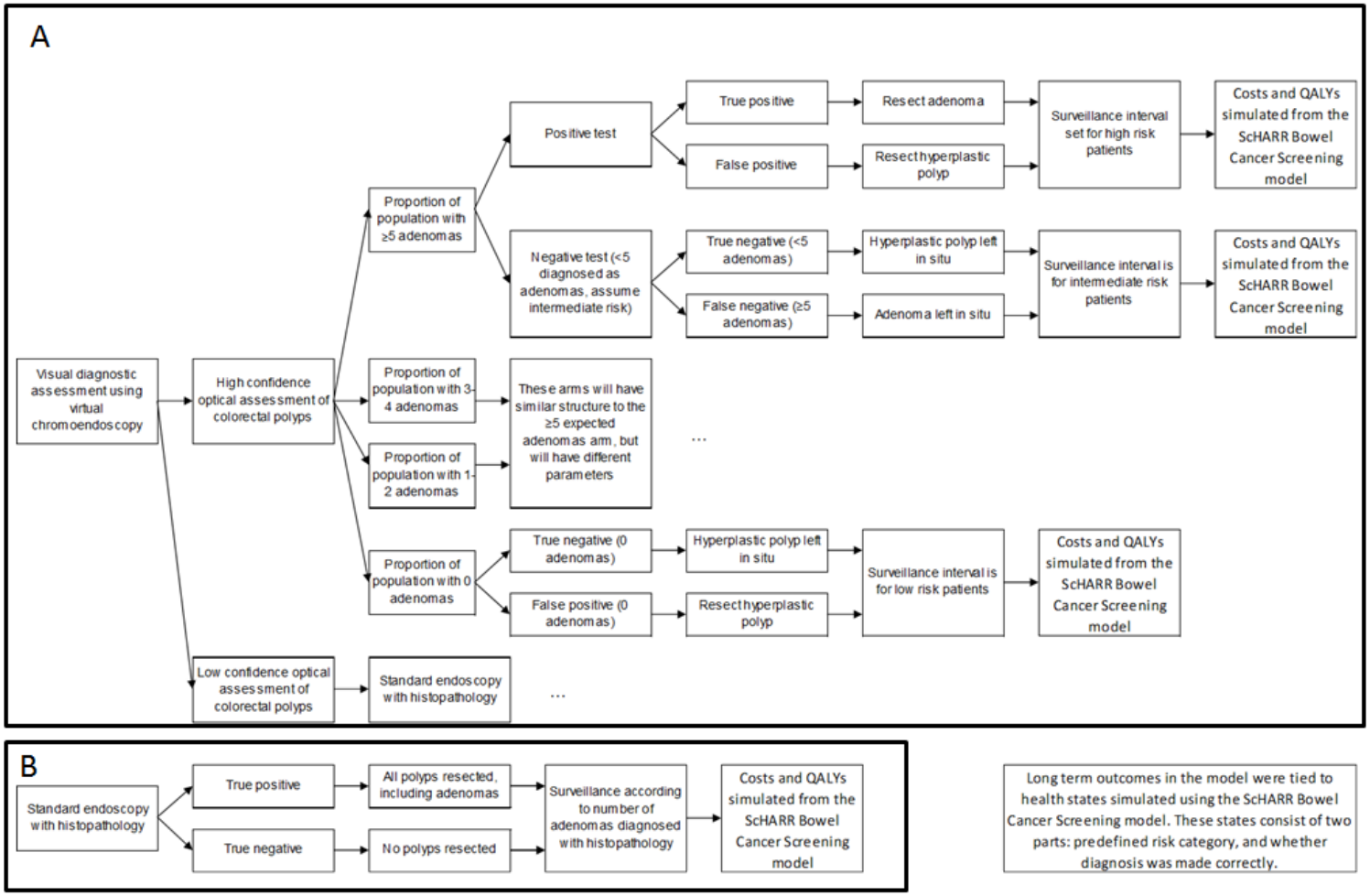
Firstly, the cohort is divided into 4 risk categories based on the number of adenomas that they have:

- no adenomas
- low risk (1 to 2 adenomas)
- intermediate risk (3 to 4 adenomas)
- high risk (5 or more adenomas)

The model then calculates the proportion of patients in each category expected to have the correct classification of polyps and surveillance interval assigned, and the proportions expected to have an incorrect classification of polyps and an incorrect surveillance interval assigned. With a virtual chromoendoscopy strategy, the following errors could lead to an incorrect surveillance interval (too long or too short) being assigned in the model:

- 1 or more hyperplastic polyps might be misclassified as an adenoma and so be unnecessarily resected.
- 1 or more adenomas might be misclassified as a hyperplastic polyp and left in place.

Figure 8 Decision tree structure



In total there are 6 main diagnostic outcomes as follows:

- correct polyp diagnosis (correct surveillance interval assigned)
- missed adenoma (correct surveillance interval assigned)
- missed adenoma (incorrect surveillance interval assigned – too long)
- hyperplastic polyps resected (correct surveillance interval assigned)
- hyperplastic polyps resected (incorrect surveillance interval assigned – too short)
- missed adenomas and hyperplastic polyps resected (correct surveillance interval)

These possible diagnostic outcomes are listed in more detail in table 32 on page 144 and figure 31 on page 145 of the diagnostics assessment report. The probability of being assigned to each diagnostic outcome depends on the diagnostic accuracy data and the number of adenomas and hyperplastic polyps in each person. It is calculated using a binomial distribution equation, further detail can be found in the diagnostic assessment report starting on page 148.

The comparator arm (arm B; histopathology) of the decision tree assumes that everyone is given the correct surveillance interval.

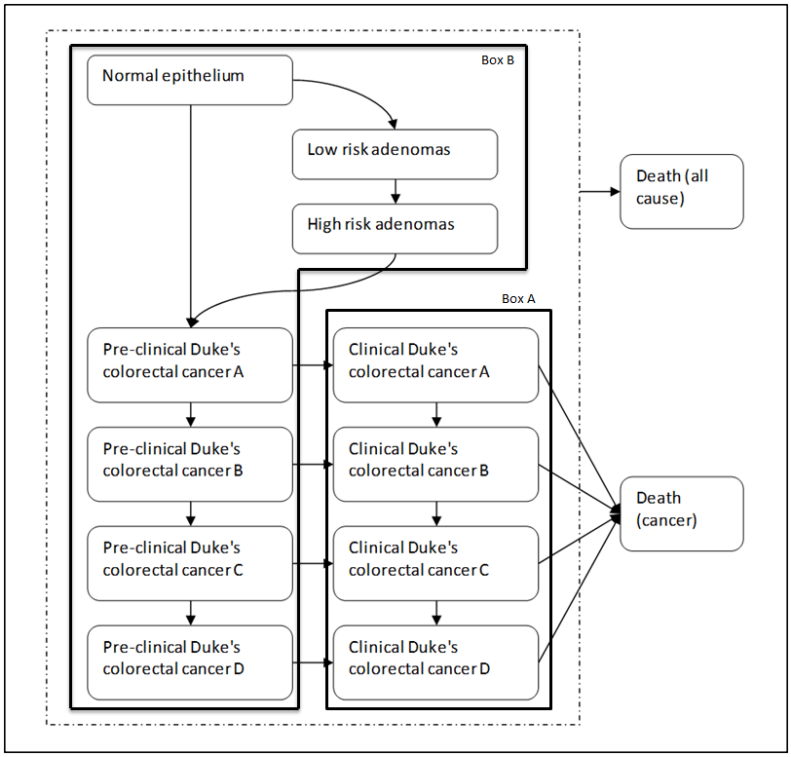
<u>The School of Health and Related Research (ScHARR) bowel cancer screening (SBCS) model: structure, modifications and assumptions</u>

The SBCS model is a state transition model produced by Whyte et al. It was developed to inform the Department of Health's policy on bowel cancer screening. The model was designed to assess the cost effectiveness of different screening strategies for colorectal cancer for a lifetime time horizon. The model simulates the progression of colorectal cancer in people who are eligible for the bowel cancer screening programme in England. The model takes the perspective of the NHS on costs and uses a discount rate of 3.5%

for costs and QALYs. Full details of the model and the modifications that were made are in section 5.3.2.3 starting on page 151 of the diagnostics assessment report.

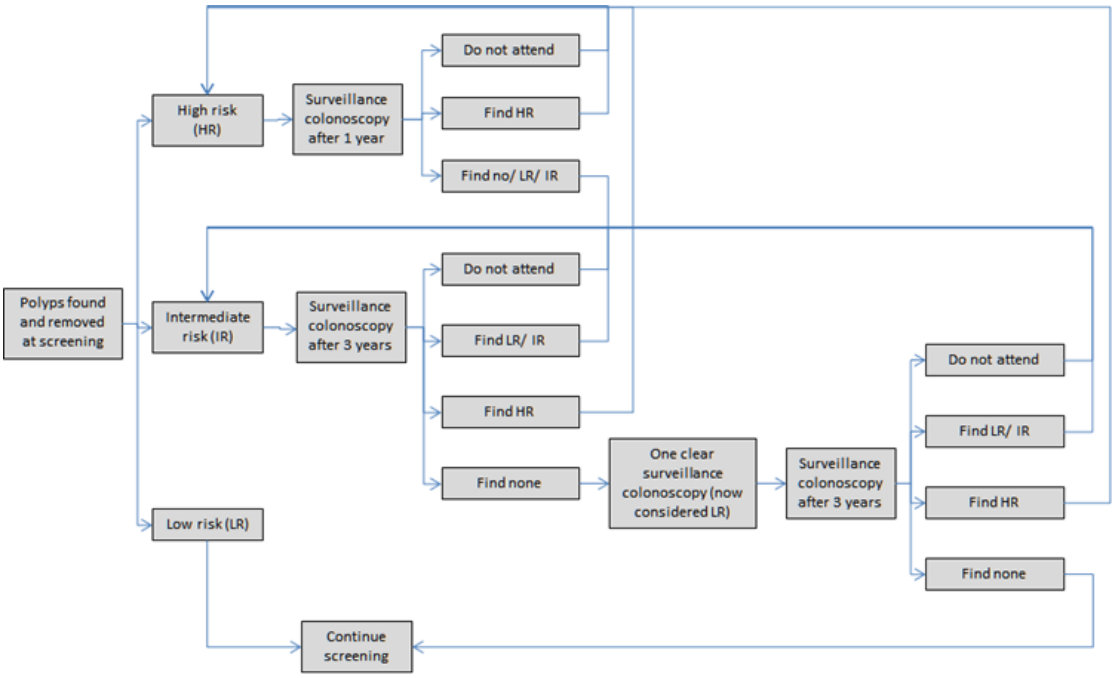
Error! Reference source not found. shows a simplified diagram of the ifferent stages of colorectal cancer in the natural history model. The cohort stays in the health states in box B until a diagnosis is confirmed. When a diagnosis of colorectal cancer is confirmed, people move to the clinical health states in box A.

Figure 9 Colorectal cancer natural history model disease progression in the SBCS model (Adapted from Whyte and colleagues)



The post-screening surveillance model pathway is shown in figure 10. The pathway shows how people taking part in the screening programme can move through the SBCS model. People are invited to routine screening if they are found to be at low risk of colorectal cancer or if they have not had any adenomas identified after 2 surveillance colonoscopies.

Figure 10 SBCS surveillance colonoscopy pathway



The following changes were made to the model for the assessment:

- Colonoscopy and adverse-event costs were updated to 2014/15 costs.
- The screening costs were updated.
- Adenoma recurrence rates were adjusted to model people with higher disease risk and people with adenomas left in the body.

The following assumptions were made so that the long-term results from the SBCS model could be used to assess the virtual chromoendoscopy tests:

- Surveillance is done using standard colonoscopy without virtual chromoendoscopy, therefore:
  - the training costs for virtual chromoendoscopy are not taken into account for this part of the model.
  - The specificity and sensitivity of standard colonoscopy for detecting adenomas was used. The specificity is assumed to be 1 and the sensitivity was assumed to vary based on the risk category; 0.77 for low-

risk adenomas and 0.98 for intermediate- and high-risk adenomas. Histopathology is assumed to correctly diagnose 100% of adenomas that are detected by standard colonoscopy, but not all adenomas will be detected.

- It is assumed that only adenomatous polyps are resected and sent to histopathology. The number of adenomas detected is assumed to be 1.9 per person.

Population

The population in the base-case analysis was people taking part in the bowel cancer screening programme who have been referred for colonoscopy. In addition, the scenario analyses looked at:

- people offered colonoscopy as surveillance because they previously had adenomas removed, and
- people referred to colonoscopy by a GP because of symptoms of colorectal cancer.

Patients were only included if they had at least 1 diminutive polyp, and were excluded if they had 1 or more non-diminutive polyps.

Diagnosis strategy

Two different diagnostic strategies were explored in the economic analyses, the virtual chromoendoscopy strategy (used in the base case) and the DISCARD strategy (Detect, InSpect, ChAracterize, Resect, and Discard; used in some scenario analyses). The criteria common to both strategies were that diminutive polyps:

- in the whole colon are optically characterised using virtual chromoendoscopy
- diagnosed with high confidence as adenomas are resected and discarded
- diagnosed with low confidence are resected and sent to histopathology.

The characteristic unique to the virtual chromoendoscopy strategy was that diminutive polyps, in the whole of the colon, diagnosed with high confidence as hyperplastic are left in place.

The characteristics unique to the DISCARD strategy were that diminutive polyps:

- in the proximal colon characterised with high confidence as hyperplastic are resected and discarded.
- in the rectosigmoid colon diagnosed with high confidence as hyperplastic are left in place.

Model inputs of the decision tree

The model inputs used by the EAG were taken from various sources, including routine sources of cost data, published literature and the clinical effectiveness review and meta-analyses. The parameters used in the decision tree model can be seen in section 5.4 starting on page 157 of the diagnostic assessment report in tables 37 to 46.

Prevalence of adenomas

The prevalence of adenomas was estimated for 3 populations: the screening population (base case), the surveillance population (scenario analysis) and the symptomatic population (scenario analysis).

The distribution of adenomas in the bowel screening population was taken from a published study by Raju et al. (2013) that retrospectively analysed data from a US colon cancer screening programme. The distributions of adenomas are reported in table 3.

The EAG was unable to find any studies reporting on the distribution of adenomas in the surveillance population for all risk classifications, but several studies were found that reported on the distribution for specific subgroups only. The proportion of people with no adenoma at follow-up surveillance was

assumed to be 53.3%, which was taken from a large study by Martinez et al. (2009). The remaining people were allocated to low-risk, intermediate-risk and high-risk categories according to the proportions taken from the screening population. The resulting distributions of adenomas are shown in table 3.

The EAG identified 1 relevant study describing the proportion of people in the symptomatic population, who had different levels of adenoma risk (McDonald et al. 2013). The study included a small number of patients with irritable bowel syndrome, so these were excluded from the calculation of the adenoma risk. The distributions of adenomas are shown in table 3.

Table 3 Proportion of people by risk category for screening, surveillance and symptomatic population

	Screening population	Surveillance population	Symptomatic population
No adenoma	0.302	0.533	0.782
Low risk	0.535	0.358	0.125
Intermediate risk	0.107	0.072	0.061
High risk	0.056	0.037	0.032

Diagnostic accuracy

Data on diagnostic accuracy were taken from the clinical-effectiveness review and meta-analysis for i-scan, NBI and FICE, as shown in table 4. Data were used for polyps in the whole colon that were characterised with high confidence in the base-case analysis for NBI and i-scan. Data were used for polyps in the whole colon that were characterised with any level of confidence in the base-case analysis for FICE. The comparator, histopathology, was assumed to be 100% accurate.

Table 4 Sensitivity and specificity for virtual chromoendoscopy technologies

Parameter	Value	Lower 95% CI	Upper 95% CI	Source
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 of polyp characterisations made with low confidence	0.214	0.21	0.22	EAG literature review[a]
[a] The average value from 12 NBI studies that were included in the literature review. Data were not available on the proportion of polyp characterisations made with low confidence for FICE and i-scan.				
Abbreviation: CI, confidence interval; FICE, Flexible Spectral Imaging Colour Enhancement; NBI, Narrow Band Imaging.				

Adverse events

The probabilities of adverse events occurring during colonoscopy were assumed to be 0.003 for hospitalisation for bleeding with polypectomy, 0.003 for perforation with polypectomy, and 0.052 for death for patients with perforation during polypectomy. These values were taken from published values used in the SBCS model.

Costs

For the base-case analysis, the costs of colonoscopy, polypectomy, adverse events and histopathology were taken from the NHS reference costs for 2014/15 (table 5). Training costs were assumed to be £14.72 per patient, based on the assumption that endoscopists complete 150 endoscopies per

year and that training costs are equivalent to 2 days of pay (£1104). The cost of training for endoscopists in the decision tree is assumed to be a one-off cost.

Table 5 Unit costs for colonoscopy and treating adverse events

Parameter	Value	Lower 95% CI	Upper 95%CI
Cost of colonoscopy without polypectomy	£518.36	£340.89	£695.83
Cost of colonoscopy with polypectomy	£600.16	£406.24	£794.08
Cost of treating bowel perforation (major surgery)	£2,152.77	£902.21	£3,403.33
Cost of admission for bleeding (overnight stay on medical ward)	£475.54	£327.69	£623.39
Pathology cost per polyp examination	£28.82	£6.78	£50.86
Abbreviation: CI, confidence interval.			

The cost of upgrading equipment was not included in the model. It was assumed that most hospitals already had equipment with virtual chromoendoscopy technology enabled in place, and that hospitals that do not have this equipment will get it in the future as part of standard procurement. Therefore, the base-case analysis assumes that the cost of maintaining and purchasing equipment is included in the HRG cost of colonoscopy.

A cost per endoscopy was calculated for NBI, i-scan and FICE and these were included in a scenario analysis (Table 6).

Table 6 Equipment and maintenance costs per endoscopy using virtual chromoendoscopy technologies

Virtual chromoendoscopy	Total cost per endoscopy	Difference compared with average cost
NBI	£232.85	£20.55
FICE	£146.99	−£65.31
i-scan	£160.64	−£51.66
Abbreviation: FICE, Flexible Spectral Imaging Colour Enhancement; NBI, Narrow Band Imaging.		

Health-related quality of life and QALY decrements

Health-related quality of life was calculated with the SBCS model. The base-case analysis used utility values taken from a study by Ara and Brazier (2011). The model assumes a utility of 0.697 for people with cancer and a utility of 0.798 for people without cancer.

A scenario analysis was done using utility values from a study identified by the EAG through a targeted search (Farkkila et al. 2013). For the scenario analysis, it was assumed that the utility for people with cancer was 0.813 and for people without cancer was 0.850.

The EAG could not find disutility values for adverse events during polypectomy, such as bowel perforation and bleeding. Therefore, the values were taken from studies that reported on similar events. A QALY loss of 0.006 was taken from Dorian et al. (2014) for the disutility of a major gastrointestinal bleed and a QALY loss of 0.010 was taken from Ara and Brazier (2011) for the disutility of bowel perforation.

Long-term estimates of costs and QALYs

The costs and QALYs for the endpoints of the decision tree were calculated by running the SBCS model with a cohort of patients aged 65. The outcomes produced by the SBCS model can be seen in table 7.

Table 7 Expected lifetime costs and QALYs for 1 person aged 65 having colonoscopy, generated using the ScHARR bowel cancer screening model

Risk at start	Outcome	Adenomas missed	Hyperplastic polyps resected	Surveillance interval	Costs £	QALYs[a]
LR (0)	CD	None	None	Invited for screening	109	11.26653
	HPRC	None	1 or more	Invited for screening	109	11.26653
LR	CD	None	None	Invited for screening	109	11.26653

(1 to 2)	HPRC	None	1 or more	Invited for screening	109	11.26653
	HPRI	None	1 or more	3-year surveillance	1075	11.29947
	MAI[a]	1 or more	None	Invited for screening	250	11.26399
	MAC[a]	1 or more	None	Invited for screening	250	11.26399
	MAHPR[c]	1 or more	1 or more	Invited for screening	250	11.26399
IR (3 to 4)	CD	None	None	3-year surveillance	1097	11.29934
	HPRC	None	1 or more	3-year surveillance	1097	11.29934
	HPRI	None	1 or more	Annual surveillance	1577	11.32057
	MAI[c]	1 or more	None	Invited for screening	250	11.26399
	MAC	1 or more	None	3-year surveillance	1161	11.29891
	MAHPR	1 or more	1 or more	3-year surveillance	1161	11.29891
HR (5 or more)	CD	None	None	Annual surveillance	1584	11.30252
	HPRC	None	1 or more	Annual surveillance	1584	11.30252
	HPRI	None	1 or more	Annual surveillance	1584	11.30252
	MAI	1 or more	None	3-year surveillance	1161	11.29891
	MAC	1 or more	None	Annual surveillance	1681	11.30152
	MAHPR	1 or more	1 or more	Annual surveillance	1681	11.30152

[a] Results for patients with missed adenomas adjusted so that costs and QALYs are less favourable than if all adenomas had been removed with the same follow-up.

Abbreviations: CD, correct diagnosis; HPRC, hyperplastic polyp resected (correct surveillance); HPRI, hyperplastic polyp resected (incorrect surveillance); HR, high risk; IR, intermediate risk; LR, low risk; MAC, missed adenoma (correct surveillance); MAHPR – missed adenoma and hyperplastic polyp resected; MAI, missed adenoma (incorrect surveillance); QALY, quality-adjusted life year.

Base-case results

The following assumptions were applied in the base-case analysis:

- The long-term cost and QALY outcomes were estimated using the SBCS model, which assumed that standard colonoscopy with histopathology assessment of all polyps was used for follow-up surveillance.

- The probability of detecting a polyp did not change after a polyp had been detected in a person.
- Studies did not report on the relationship between diagnostic accuracy and assigning people to the correct surveillance intervals, therefore the following was assumed:
  - diagnostic accuracy data for individual polyps was applied to the whole person
  - the adenoma to hyperplastic polyp ratio was assumed to be the same for each risk category.
- The screening test used in the SBCS model was the guaiac-based faecal occult blood test.
- Only diminutive polyps were assessed, people with polyps larger than 5 mm were not included in the model
- The model does not differentiate between depressed polyps or sessile serrated polyps, beause diagnostic accuracy data were not available for these polyps.
- The cost of purchasing, running and maintaining NBI, FICE and i-scan was the same.
- Polyps can be diagnosed with high confidence in the whole colon.
- The likelihood of being assigned the correct surveillance interval was based on the number of polyps and adenomas that the patient had and the diagnostic accuracy data for individual polyps.
- The proportion of polyps assessed with low confidence (21%) is assumed to be the same for NBI, FICE and i-scan.
- The disutility for bleeding is assumed to be similar to a major gastrointestinal bleed.
- The disutility for perforation is assumed to be the same as for a stomach ulcer, abdominal hernia, or rupture.

The results of the base-case analysis can be seen in Table 8. Pairwise analyses compared each of the 3 technologies in turn (i-scan, FICE and NBI) with histopathology. Results showed that NBI and i-scan dominated histopathology, that is, they are cheaper and more effective than histopathology. FICE is cost saving and less effective than histopathology, with an ICER of £671,383 saved per QALY lost.

The differences in costs and QALYs between the tests were very small. The differences in incremental QALYs ranged from −0.0001 when FICE was compared with histopathology to 0.0007 when i-scan was compared with histopathology. The differences in costs ranged from −£87.70 when FICE was compared with histopathology and to −£73.10 when NBI was compared with histopathology.

Table 8 cost-effectiveness results of the lifetime economic model

	Costs	Inc Costs	QALYs	Inc 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[a]
Histopathology	£988.95		11.2703		
i-scan	£909.74	−£79.21	11.2709	0.0007	Dominates
[a] Incremental cost saving per QALY lost					
Abbreviations: FICE, Flexible Spectral Imaging Colour Enhancement; Inc, incremental; NBI, Narrow Band Imaging; QALY, quality-adjusted life year;					

Analysis of alternative scenarios

The EAG did 12 scenario analyses. Fewer scenario analyses were done for FICE, because data were unavailable. The scenarios were:

- Base case: the virtual chromoendoscopy strategy was applied to diminutive polyps in the whole colon for characterisations made with high confidence.
- Scenario 1: the risk-category distributions for the cohort were changed to reflect a population that were having colonoscopy as surveillance.
- Scenario 2: the risk-category distributions for the cohort were changed to reflect a cohort with symptoms.
- Scenario 3: the discard strategy was applied and diagnostic accuracy data were used for high-confidence characterisations in the rectosigmoid colon only.
- Scenario 4: the discard strategy was applied and diagnostic accuracy data were used for high-confidence characterisations in the whole colon.

- Scenario 5: the discard strategy was applied and diagnostic accuracy data were used for all levels of confidence in characterisation in the whole colon.
- Scenario 6: the virtual chromoendoscopy strategy was applied and diagnostic accuracy data were used for characterising polyps made with any level of confidence.
- Scenario 7: varied the cost of the equipment, so that the differences in prices between the technologies were taken into account.
- Scenario 8: alternative utility values were used.
- Scenario 9: used pooled diagnostic accuracy data for all virtual chromoendoscopy technologies
- Scenario 10: used diagnostic accuracy data from studies that reported data for endoscopists experienced in using NBI for the whole colon
- Scenario 11: used diagnostic accuracy data from studies that reported data for endoscopists experienced in using NBI for the rectosigmoid colon
- Scenario 12: the likely effect on the model results if everyone had virtual chromoendoscopy as follow-up surveillance.

Further details of the scenario analyses can be seen in starting on page 175 of the diagnostic assessment report.

Results of the scenario analyses show that NBI and i-scan were dominant in all scenario analyses when compared with histopathology. For the pooled analysis in scenario 9, virtual chromoendoscopy technologies were dominant in comparison to histopathology.

When FICE was compared with histopathology it was cost-effective in all scenario analysis. In scenarios 1, 2 and 5, FICE was cheaper and more effective than histopathology and therefore was dominant. In scenario 7, FICE was cheaper and less effective than histopathology and had an ICER of £963,335 saved per QALY lost. In scenario 8, FICE was cheaper and slightly

less effective compared with histopathology and had an ICER of £1,273,941 saved per QALY lost.

The results of scenario analyses 10 and 11 (experienced endoscopist for NBI) were similar to the base-case analyses for virtual chromoendoscopy and NBI dominated histopathology.

The effect of using virtual chromoendoscopy (NBI) for surveillance (scenario 12) was small, this was estimated to increase cost savings by £20 and increase QALYs gained by 0.0003. Scenario 12 estimated the effect of using virtual chromoendoscopy in people having surveillance; as in the base case, surveillance is assumed to be carried out using standard colonoscopy. For example, the additional cost per patient having histopathology compared with NBI was estimated to be £81.82 for patients at high risk and the additional loss of QALYs was estimated to be −0.0007. For this analysis, the proportion of people having follow-up colonoscopy and the time until surveillance colonoscopy was estimated by the EAG. The parameters used can be seen in table 57 on page 180 of the DAR.

Sensitivity analyses

One-way deterministic sensitivity analyses

The EAG did one-way sensitivity analyses by varying the inputs of the decision tree (see tables 50 and 51 starting on page 171 of the diagnostic assessment report). The outputs are reported as net monetary benefit using a threshold of £30,000 per QALY.

The inputs were varied using the upper and lower bound of the 95% confidence intervals identified during the clinical-effectiveness review and the economic-model inputs search. Because confidence interval values were not available, the EAG assumed ranges for the following inputs:

- proportion of low-confidence assessments
- prevalence of adenomas in patients with polyps

- average number of adenomas in patients with low-risk adenomas
- average number of adenomas in patients with intermediate-risk adenomas
- average number of adenomas in patients with high-risk adenomas.

Data were not available for the uncertainty over the long-term costs and QALYs. Therefore, the range for the sensitivity analysis was calculated for false test results by comparing the costs and QALYs gained by the false test result with the true test result. The difference between the 2 results was halved and added or subtracted from the result. For example, the long-term cost of a low-risk state with missed adenomas is £250 and the long-term cost of a low-risk state with correct diagnosis is £109. Therefore, the sensitivity analysis range was £180 to £321, all of the ranges can be seen in table 51 on page 173 of the diagnostic assessment report.

In all of the one-way deterministic analyses, NBI was both cost effective compared with histopathology at a maximum acceptable threshold of £30,000 per QALY and the dominant strategy. The inputs with the largest effect on the incremental net monetary benefit were:

- pathology cost
- the probability of perforation with polypectomy
- the proportion of people who die from perforation
- the long-term QALY estimate for the intermediate-risk missed adenoma health state.

The results of the one-way deterministic sensitivity analyses show that FICE was cost-effective when compared with histopathology at a maximum acceptable threshold of £30,000 per QALY, because the net monetary benefit is negative for all analyses. The inputs with the largest effect on the incremental net monetary benefit were:

- pathology cost
- the probability of perforation with polypectomy

- the proportion of patients who die from perforation
- the proportion of low-confidence characterisations.

The results of the one-way deterministic sensitivity analyses show that i-scan was cost-effective compared with histopathology at a maximum acceptable threshold of £30,000 per QALY in all sensitivity analyses. The inputs with the largest effect on the incremental net monetary benefit were:

- pathology cost
- the probability of perforation with polypectomy
- the proportion of patients who die from perforation
- the proportion of low-confidence characterisations.

Probabilistic sensitivity analyses

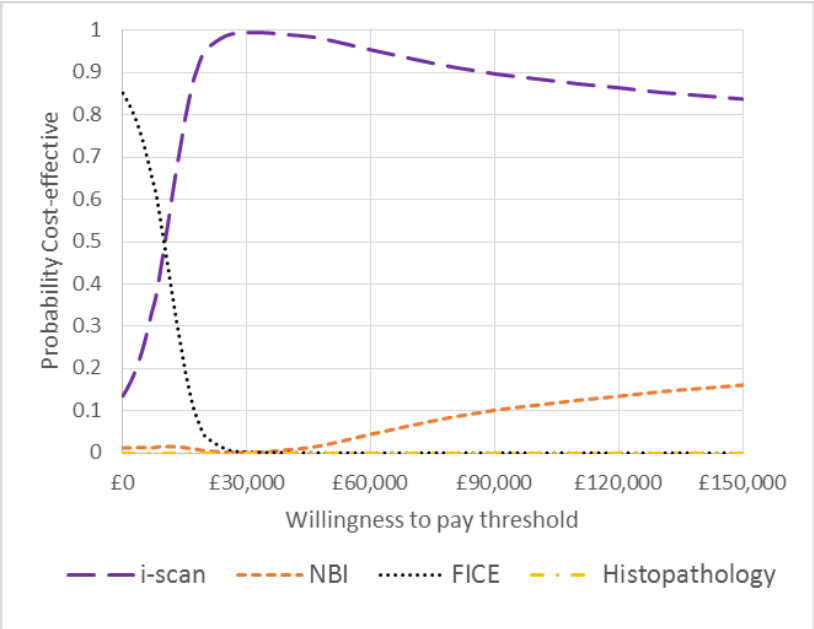
The EAG did a probabilistic sensitivity analysis by varying the inputs of the decision tree, using the distributions in appendix 9 of the diagnostic assessment report. The analysis was done by running the model 5,000 times, each time the inputs were varied according to the distribution of the input. The analyses were done on the base-case analysis.

The cost of colonoscopy between different technologies is assumed to be the same in all probabilistic sensitivity analysis.

Probabilistic sensitivity analysis results

The base-case probabilistic sensitivity analysis found that at a maximum acceptable ICER of £20,000 per QALY, i-scan was cost-effective in 85.2% of the analyses and at a maximum acceptable ICER of £30,000 per QALY it was cost-effective in 99.5% of the analyses. FICE and NBI were dominated by i-scan in the analysis.

Figure 11 Cost-effectiveness acceptability curves (base case)



3 Summary

From the clinical-evidence review it was unclear whether the technologies met the preservation and incorporation of valuable endoscopic innovations (PIVI) criteria, for using these technologies with a resect and discard strategy. The studies that were included in the review suggest that the negative predictive value for NBI and i-scan could be more than 90%. But there were a small number of studies.

The effect of study setting was not investigated and so the generalisability of the results to different settings is unknown. The clinical-effectiveness results were not comparable between the technologies, because of the heterogeneity between the studies including, study setting and level of endoscopist experience in using virtual chromoendoscopy. Therefore, conclusions could not be drawn on which of the technologies performed the best.

The evidence that was reviewed suggested that virtual chromoendoscopy is most effective when done by experienced and trained endoscopists. But more

research is needed to further understand the relationship between endoscopist experience and health outcomes.

The economic analyses (base-case analysis, sensitivity analyses and scenario analyses) found that all 3 virtual chromoendoscopy technologies were cost-effective compared with histopathology. The base-case economic analysis found that i-scan and NBI were both cheaper and more effective than histopathology. FICE was cheaper and less effective when compared with histopathology and had an ICER of £671,383 saved per QALY lost.

The one-way deterministic sensitivity analyses found that the parameters that had the most influence on the cost effectiveness of the tests were: pathology cost, the probability of perforation with polypectomy, and the proportion of patients who die from perforation.

4 Issues for consideration

Clinical effectiveness

The generalisability of the results of this assessment to different settings is unknown. Many of the studies included in the clinical-effectiveness systematic review were done in specialist centres and in some cases by 1 endoscopist. Also, the effect of the study setting on diagnostic accuracy estimates was not assessed. The major study applicable to the UK and multicentre settings was not included in the review (DISCARD 2), because only 22% of the colonoscopies were done using high definition equipment.

The evidence base for FICE and i-scan was limited and there is also uncertainty over the results of the analysis for these technologies. All of the studies included for i-scan and FICE were done in single centres. Additionally, most of the studies were done by 1 endoscopist (4 out of 5 i-scan studies and 2 out of 3 FICE studies).

All of the i-scan studies included experienced endoscopists in single centres, often described as academic or specialist centres. The accuracy 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.

The diagnostic accuracy data on FICE does not include data on polyp characterisations made with high confidence. So these cost-effectiveness results are not directly comparable with those of the other virtual chromoendoscopy technologies in which polyp characterisations made with high confidence were used in the base case.

Cost effectiveness

The SBCS model (state transition model) results were produced and validated externally. The EAG were unable to critically appraise the model and validate the results, because they did not have access to the model. There is unknown uncertainty over the long-term costs and QALYs. Also, virtual chromoendoscopy is not included in the SBCS model, it is assumed that standard white light endoscopy and histopathology is used in surveillance for all arms of the model. This means that ongoing training costs for virtual chromoendoscopy are not included in the model and the clinical effect of using virtual chromoendoscopy for surveillance has not been assessed. Therefore, the current cost savings for virtual chromoendoscopy are uncertain and the health benefits may have been overestimated. A scenario analysis to estimate the effect of relaxing this assumption on the results found that it was small.

The QALY gain for virtual chromoendoscopy compared with histopathology is driven by the reduction in adverse events associated with polypectomy, because using a discard strategy means that fewer polyps would need to be resected. The data for the risk of these adverse events were taken from a study of polypectomy of polyps of all sizes, not limited to polyps of 5 mm or less. Expert clinical opinion suggests that the risk of these adverse events

occurring in colonoscopies with polypectomy of polyps 5 mm or less is negligible, therefore the QALY gain may be overestimated. The adverse-event model inputs were varied in one-way sensitivity analyses and the model was found to be sensitive to these inputs. When the risk of adverse events associated with polypectomy was lower, the QALYs gained for virtual chromoendoscopy compared with histopathology were reduced, but virtual chromoendoscopy remained dominant over histopathology.

In the model, the adverse events of hospitalisation for bleeding, perforation and death from perforation are only assigned to colonoscopies during which polypectomy is done. Expert clinical opinion suggests there is a risk associated with all colonoscopies, that is, the adverse events are not limited to colonoscopies in which polypectomy is performed. These adverse-event risks are not included in the model, therefore potential disutility associated with colonoscopies are not fully captured.

The SBCS model follows the national bowel cancer screening guidance for adenoma surveillance, in which people identified as being at low risk after a screening colonoscopy return to routine screening. The NICE guideline on colonoscopic surveillance, which is for people who have had adenomas removed, recommends that colonoscopy at 5 years is considered if a person is identified to be at low risk of colorectal cancer (1 or 2 adenomas smaller than 10 mm). Therefore, the model pathway may not accurately reflect clinical practice in the NHS for people who are offered surveillance after removal of adenomas and are at low risk of colorectal cancer.

The SBCS model assumes that for each person, 1.9 adenomas are resected and sent to histopathology. This may underestimate histopathology costs in the comparator arm, because the histopathology costs associated with hyperplastic polyps are not included in the SBCS model. Therefore, the comparator costs are likely to be underestimated in the SBCS model.

The initial purchasing costs for equipment for hospitals that do not already have the necessary equipment have not been included in the model. This is because the proportion of hospitals that would need an equipment upgrade is unknown. It is assumed that hospitals already have equipment with virtual chromoendoscopy technology enabled or will get this in the future as part of standard procurement.

Expert opinion is that sometimes in current practice diminutive polyps diagnosed as hyperplastic may be left in place in the rectosigmoid area, using conventional white light to assess the polyps. However, it was beyond the scope of the assessment to look at the clinical effect of virtual chromoendoscopy compared with conventional white light for assessing polyps during a colonoscopy. Therefore, if some polyps are being left in place in current practice rather than all polyps being removed and sent for histological assessment then the cost savings associated with virtual chromoendoscopy could be over estimated.

The model assumed that histopathology was 100% accurate, however it is likely to be lower than 100% in clinical practice. Therefore, virtual chromoendoscopy may be more cost effective than the base-case ICERs suggest.

The model assumes that only diminutive polyps are identified. This means that the effect of having a mixture of large and small polyps has not been assessed. It is possible that having a mixture of polyps could also be associated with a cost saving from reductions in histopathology.

The adenoma to hyperplastic polyp ratio is assumed to be the same for all risk categories. Sensitivity analysis was not done to investigate the effect of changing this assumption. However, sensitivity analysis was done to look at the effect of changing the prevalence of adenomas in all risk groups and this had a large effect on the ICER.

5 Equality considerations

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

All people with cancer are covered under the disability provision of the Equality Act (2010) from the point of diagnosis. Colorectal cancer is more common in older men and women. In the UK between 2010 and 2012, bowel cancer was diagnosed in an average 43% of people aged 75 and over, and in an average of 95% of those aged 50 and over. Each of these potential equality issues are functions of the clinical condition and not the technology under assessment.

6 Implementation

6.1 Pathway

Adoption of this technology into routine clinical practice with the intention of reducing the number of unnecessary polypectomies and the number of polyps sent for histopathological assessment would be a significant change to the current patient pathway. There are concerns about the responsibility of diagnosing potentially cancerous polyps moving from histopathology laboratories to clinicians in non-specialist care, and the risk and implications if cancers are missed.

6.2 Patient confidence

People will need to be confident in the experience and performance of the endoscopist if there is a move away from all polyps being removed and having histopathological assessment. Some people may have concerns and may not agree to this.

6.3 Training

Clinical experts note that achieving competency in real-time optical diagnosis using virtual chromoendocopy is affected by previous experience, motivation and enthusiasm for this technology. They report that it can take up to 6 months to achieve competency and consistently high performance. Further, over time performance may decrease, particularly for specificity, so ongoing training will be needed to maintain performance.

6.4 Quality assurance and governance

Clinical experts consider that clinicians using virtual chromoendoscopy would need to be accredited and performing at least 150 colonoscopies with real-time optical assessment of colorectal polyps per year to maintain competency. The experts advise that accreditation for using virtual chromoendoscopy could be easily included in the current endoscopic accreditation programme.

6.5 Quality of images recorded and stored

Clinical experts have noted that the quality of the images stored is suboptimal when compared with the image the clinician sees on the screen at the time of assessment. There will need to be an accurate process for storing and linking the images to patient files and the ability to recall specific images to enable re-evaluation.

7 Authors

Jessica Maloney
Topic Lead

Frances Nixon
Technical Adviser

October 2016

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Southampton Health Technology Assessments Centre (SHTAC):

Virtual chromoendoscopy for the real-time assessment of colorectal polyps in vivo: a systematic review and economic evaluation. Southampton Health Technology Assessments Centre (SHTAC), 2016.

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- Aquilant Endoscopy
- Olympus Medical
- Pentax Medical

Other commercial organisations:

- None

Professional groups and patient/carer groups:

- British Society for Gastroenterology
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Bowel Cancer UK

Research groups:

- None

Associated guideline groups:

- None

Others:

- Department of Health
- Healthcare Improvement Scotland
- NHS England
- Welsh Government

Appendix B: Glossary of terms

Chromoendoscopy
Dyes are used in the gastrointestinal tract during endoscopy to enhance visualisation of the tissue

Colonoscopy
A procedure which allows a clinician to look at the inner lining of the large intestine using a thin flexible tube called a colonoscope

Colorectal polyps
A fleshy growth occurring on the lining of the colon or rectum

Diminutive polyps
Polyps between 1 and 5 mm in size

Faecal occult blood test
A test which detect small amounts of blood in faeces

Histopathology
The study of diseased tissue, including examination under the microscope

PIVI
The PIVI (Preservation and Incorporation of Valuable endoscopic Innovations) initiative is an American Society for Gastrointestinal Endoscopy programme

Polypectomy
Removal of polyps

Proximal colon
The first and middle parts of the colon, which includes the cecum (where the small intestine joins the colon), the ascending colon (the right side) and the traverse colon (the part that goes across the body connecting right and left)

Rectosigmoid
The lower part of the sigmoid colon (the S-shaped part of the colon that connects the descending colon [left side] to the rectum) and the upper part of the rectum