10 APPENDICES

Appendix 1 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 2 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 <u>majority</u> 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**

<u>Decision rules</u>

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 3 Data extraction tables.

One data extraction form is provided here as an example in this shortened version of Appendix 3. The full data extraction tables are available for every included study from the report authors.

Aihara et al.[54]

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	**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	**Number of participants:** 203, of whom 67 were found to have polyps **Sample attrition/dropout:** Not explicitly stated, but assumed to be zero.	**Primary outcome of study:** The threshold score on the polyp scoring system that provided the highest negative predictive value (NPV).

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.	endoscopist switched to NBI to score the polyp (scores were compared to histopathological diagnoses to determine the threshold score). **Reference standard:** Histopathology	**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.	**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.[37] adaptation of the QUADAS Tool[38])

	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	Pathologists were blinded to the	Yes

	without knowledge of the results of the index test?	endoscopic findings.	
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.

Appendix 4 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	Abstract- insufficient details

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.	
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	Intervention (not real-time assessment)

light. *World Journal of Gastrointestinal Endoscopy* 2015;7(5):555-62	
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 $\leqslant$ 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 $\leqslant$ 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	Intervention (used

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.	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 $\leqslant$ 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,	Outcomes

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	
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*	Comparator (histology not compared to VCE

2009;21 Suppl 1:S113-20.	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	Intervention (used magnification)

differentiating colorectal polyps. *Gastrointestinal Endoscopy* 2015;81(5 suppl. 1):Ab259-ab60	
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 5 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 67 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	Prospective study of real-time diagnosis of colorectal polyps using narrow-band imaging: Gangnam-ReaDi	August 2016

Republic of Korea	Study	N = 5000

Table 68 Identified conference abstracts reporting recently complete or ongoing studies not yet published in full

Reference	Title
Belderbos 2015[150]	The accuracy of real-time probe based confocal LASER endomicroscopy for differentiation of colorectal polyps during colonoscopy
Kaltenbach 2014[151]	Gastroenterology trainees can perform real time optical diagnosis of diminutive colorectal polyps using narrow band imaging
Kheir 2016[152]	Optical diagnosis of diminutive colorectal polyps by non-academic general gastroenterologists using non-magnifying narrow band imaging (NBI): A prospective study
Klein 2014[153]	Computerized, image analysis of diminutive polyps during colonoscopy-preliminary results of a feasibility study
Lee[154]	Learning curve for optical biopsy using narrow band imaging-can real-time training improve accuracy?
Lee 2015[155]	Learning curve for optical biopsy using narrow band imaging (NBI) - Can real-time training improve accuracy?
Madacsy 2015[156]	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 2015[157]	Real-time biopsy of colorectal polyps = 6 mmusing fice, I-scan and NBI technologies: Experience of a young endoscopist
Neumann 2015[158]	Development and validation of a simple classification system for in vivo diagnosis of colorectal polyps using digital chromoendoscopy - The visible study
Paggi 2014[159]	Is it really so easy to learn histologic characterization of diminutive polyps by narrow band imaging? Preliminary results of endoscopists' and nurses' performances.
Rastogi 2014[160 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 2014[161 a]	Prediction time for characterizing diminutive (% 5mm) polyp (DP) histology with NBI during colonoscopy is a marker for high confidence (HC) diagnosis and accuracy

Reference	Title
Rastogi 2014[162] [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 2014[163]	In vivo diagnosis of colorectal polyps by GI endoscopists using HD narrow-band imaging
Staiano 2016[164]	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 2015[166]	Significance of Endoscopic Mucosal Surface Features in Diagnosing Colorectal Polyps

[a] These references are possibly linked to the Gupta 2012 study[56] included in this review, but this is not clear.

Appendix 6 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 7 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**	Future costs and life years were discounted at 3% per year

<table>
<tr><td></td><td>(rate)</td><td></td></tr>
<tr><td>11</td><td>Costing year, currency</td><td>Not reported</td></tr>
<tr><td>12</td><td>Population</td><td>Hypothetical cohort of 100,000 50 year old persons in United States who underwent a colonoscopy for CRC screening.</td></tr>
<tr><td>13</td><td>Intervention(s), comparator(s)</td><td>Narrow band imaging versus colonoscopy versus no screening</td></tr>
<tr><td>14</td><td>Intervention effect</td><td>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,</td></tr>
<tr><td>15</td><td>Health state utilities</td><td>HRQoL not included</td></tr>
<tr><td>16</td><td>Intervention cost</td><td>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.</td></tr>
<tr><td>17</td><td>Indirect costs</td><td>None listed</td></tr>
<tr><td>18</td><td colspan="2">Results
<table>
<tr><td>Discounted</td><td>No screening</td><td>Colonoscopy</td><td>Colonoscopy with resect and discard</td><td>Incremental</td><td>ICER</td></tr>
<tr><td>Cost/person</td><td>$3390</td><td>$3222</td><td>$3197</td><td></td><td></td></tr>
<tr><td>Relative efficacy</td><td>-</td><td>51 days / person</td><td>51 days / person</td><td></td><td></td></tr>
</table>
</td></tr>
</table>

	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 8 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 9 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

Parameter	Mean value	distribution	alpha	beta
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 10 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 inTable 70, the proportion of patients with one or more polyps and who have no adenomas is 30.2%.

Table 69 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 70 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 71 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 11 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 66 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 72 Equipment and maintenance costs for virtual chromoendoscopy technologies

Item	NBI	FICE	i-scan
Processor / light source cost	£40,395.00	£28,500.00	[redacted]
Scope cost	£38,660.00	£25,712.50	[redacted]
Scope maintenance per year	£4,805.00	£2,900.00	[redacted]
System maintenance per year	£3,525.00	£2,200.00	[redacted]

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 $\frac{Cost\ of\ system\ and\ scope}{Annuity\ factor}$, where the annualisation factor = $1 + \frac{1-(1-r)^{1-n}}{r}$ = 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 73 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