NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
British Society of Gastroenterology	1.	20	Conclusions	It is concluded that NBI and FICE meet PIVI standards for a resect and discard policy, but it is unclear how the findings generalise to UK practice. The only UK NHS "real world" (as opposed to specialist centre) study (Rees 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.) is excluded from analysis. The findings did not meet PIVI criteria and are therefore relevant to the cost effectiveness analysis, and applicability, of this technology. This was an NIHR-HTA funded trial conducted in NHS district general hospitals and is therefore potentially more relevant to clinical practice than those conducted in specialist centres, by specialist operators, in the UK or abroad. The reason given for exclusion was that the majority of endoscopies were not HD, but analysis in the paper showed no advantage in sensitivity or specificity in those HD colonoscopies.	It is correct that the chief reason for excluding the DISCARD 2 study was that 78% of colonoscopies were not HD. However, the study also focussed on the diagnosis of small (<10 mm) polyps and although there was some reporting for a subgroup of diminutive polyps these were defined as <6mm which differs to other evidence included in the review (where diminutive polyps were ≤5mm). Furthermore polyp level outcomes of relevance to the review (e.g. sensitivity and specificity) were not reported separately for diminutive polyps.
Olympus	2	49-70	4.1.1	The SLR appears to have missed some key clinical trials and the rationale for this is unclear. Comparison with the ASGE 2015 SLR[1] – a recently published medical association paper – highlights that while the majority of the NBI studies included by ASGE were considered in the present SLR, the ASGE meta-analysis identified several additional studies for FICE and i-Scan that were not incorporated in the present SLR. Furthermore, there are several other studies that were published after the ASGE SLR which are not considered by the present SLR. While differences in the inclusion / exclusion criteria may account for some of these discrepancies, it is unclear why others were missed which may	We did check that our searches had identified all the references to studies reported in the ASGE systematic review as part of our standard procedures. Therefore all the ASGE systematic review references were identified and screened by us.

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				bias the results, such as the following papers which are not mentioned anywhere in the report: • Repici A *et al.* Narrow-band imaging international colorectal endoscopic classification to predict polyp histology: REDEFINE study (with videos). Gastrointest Endoscp 2016;84(3):479-86 *[epub ahead of print available in February 2016; poster also presented at DDW 2015]* • Schachshal G *et al.* Endoscopic versus histological characterisation of polyps during screening colonoscopy. Gut 2014;63(3):458-65 *[Included in ASGE review and unclear why not captured]* • Bouwens MW *et al.* Optical diagnosis of colorectal polyps using high-definition i-scan: an educational experience. World J Gastroenterol. 2013 Jul 21;19(27):4334-43Chan	Repici A *et al.* Excluded at title and abstract screening stage. Polyps were characterised from a video library of images (i.e. not real-time characterisation). Schachshal G *et al.* Full paper screened (although record downloaded incorrectly with Mayr listed as the first author) and excluded (reason: outcomes) because results for a subgroup of diminutive (≤ 5mm) polyps were presented only for conventional colonoscopy & i-scan combined. Bouwens MW *et al.* Excluded at title and abstract screening stage. Polyps were characterised from a video library of images (i.e. not real-time characterisation).
Olympus	3	71-110	4.1.2	The meta-analyses conducted may be biased for the following two key reasons: • For NBI, they are based on data from endoscopists with varying levels of expertise while for FICE and i-Scan it is expert data only *(See below)*.	Meta-analyses were conducted on the same basis for each technology i.e. including all available data. The EAG did not set out to select expert only data for

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				• The two studies incorporated into the i-Scan meta-analysis have limitations which may make them unrepresentative of i-Scan's real-world diagnostic capabilities *(See comment #3).* Given training is a key factor in outcomes and studies have demonstrated significantly better outcomes with NBI for trained vs. novice endoscopists – which is acknowledged throughout the report itself (e.g. Section 1.2.6) – for a fair comparison across technologies the base case and scenario analyses should be made on consistent grounds (i.e. apple-to-apple comparison). For example, including only the expert data for each of the technologies, or including all data available including mixed expertise of operators for each technology. The following options are proposed: 1) Select expert level inputs only for NBI - this would comprise the following studies if overall predictions (not only high-confidence) should be considered: • Rex DK. Gastroenterology 2009; 136:1174–1181. • Ignjatovic et al. Lancet Oncol 2009;10:1171–1178. • Rastogi et al. Am J Gastroenterol 2009;104:2422–2430. 2) Select mixed (experts and non-experts) level inputs for FICE and i-Scan and, therefore, ensure to include non-expert studies for FICE and i-Scan in the meta-analyses, such as:	the meta-analyses of FICE and i-scan (not pre-specified in the protocol). Furthermore we were not able to conclude that any of the FICE studies were conducted by experts in FICE. We are aware, however, that as a consequence of the larger evidence base, the evidence for NBI is more diverse than that for either FICE or i-scan. We have subsequently conducted a post-hoc meta-analysis restricting the NBI studies to those in which it was reported that endoscopists had expertise in the technology. To inform an additional scenario analysis using the economic model a post-hoc meta-analysis limited to high confidence characterisations of polyps in either the whole colon or in the rectosigmoid colon made by expert endoscopists has been conducted for those interventions where data are available. As stated earlier in relation to comment 2, the studies by Repici, Schachschal and

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				For FICE • Repici et al. Gastrointest Endosc. 2016;84(3):479-486.e3 For i-Scan • Schachschal et al. Gut. 2014;63(3):458-65 • Bouwens et al. World J Gastroenterol. 2013 Jul 21;19(27):4334-43. In addition, since a fair comparison between the technologies is not possible on the basis of the quality and amount of evidence, as well as aligned level of expertise, we recommend a clear statement in the executive summary and the main body of the report: *"As the model inputs for FICE and i-Scan are based on scarce evidence and biased for expert data only, they may not be reflective of real-life clinical practice and should, therefore, be interpreted with caution when the outcomes for the technologies are compared."*	Bouwens did not meet the inclusion criteria for our systematic review, for the reasons stated above. The limited availability of evidence for i-scan and FICE have already been indicated in the Abstract (p.7), Scientific summary (p.20) as well as elsewhere in the report (e.g. sections 7.1.1, 7.2.2).
Olympus	4	100-105	4.1.2	The two studies included in the i-Scan meta-analysis have limitations which may make them unrepresentative of i-Scan's real-world diagnostic capabilities: • Each paper was based on the use of i-Scan by only 1 endoscopist, meaning the report makes generalisations about its diagnostic capabilities based on a meta-analysis of the performance of two individuals and may be biased (vs. 95 endoscopists across the NBI trials incorporated into the meta-analysis)	The number of endoscopists characterising polyps was not an exclusion criterion for the review. Our report notes that 5 of the 24 studies providing data on NBI were also conducted by only 1 endoscopist. The report has contextualised the generalisability of the i-scan studies and

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				• Both papers used classification systems designed by the endoscopist for the study so are not directly comparable, nor standardised • Basford *et al.* is not representative of real-life clinical practice as each polyp was *"flushed with a solution of water, simethicone, and N-acetyl-cysteine to remove any excess stool, mucus and bubbles"* prior to undergoing diagnosis, meaning the diagnostic outcomes in this study are likely to be much higher than in a real-world setting o This potential bias appears to be further supported but the unusually high outcomes for white light endoscopy in the study which, as acknowledged by the authors in the paper, have not been reproduced by any other study Given these limitations we recommend they are explicitly outlined in section 4.1.2 and the following statement be included in the Executive Summary of the report to ensure the data can be interpreted appropriately: *"It should be noted that the clinical outcomes for i-Scan incorporated in this report and model are based on only two clinical trials which have several limitations (outlined in section 4.1.2) and, therefore, may not be representative of i-Scan's real-world diagnostic capabilities which is likely to be lower. As such, any conclusions drawn from these data should be interpreted with caution."*	indicated that that transferability of the results is unclear (p. 102; p.189, p. 203, p. 205)

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<tr><td>Olympus</td><td>5</td><td>160</td><td>5.4.1.2 (Table 39)</td><td>There is no consensus on how high confidence is defined which may, in general, influence the clinical performance of optical diagnosis. However:
The definition used in this evaluation (i.e. feasibility of optical diagnosis) is not necessarily dependent on the technology itself alone, but also on the expertise and training of the endoscopist conducting it
High confidence definitions also relate to the methodology used to characterise the polyps, such as the NICE classification which was developed specifically for NBI and serves as ‘visual criteria’ as opposed to “gut feeling”
Evidence suggests feasibility rates (high confidence levels) vary by technology (see table below) which does not appear to be appropriately captured in the existing data analyses
As such, it seems inappropriate to apply a single ‘low confidence’ prediction based on NBI data to all comparators.

Feasibility rates (high confidence) of optical diagnosis

<table><tr><td></td><td></td><td>Experts</td><td>References</td><td>Non-experts</td><td>References</td><td>Mixed</td><td>References</td></tr></table></td><td>Across the 12 NBI studies that provided data on high confidence diminutive polyp characterisations in the whole colon the proportion of high confidence decisions ranged from 72.6% to 92.5%. For i-scan there was only one equivalent study which reported 80% high confidence decisions. Due to the very limited evidence on this parameter for i-scan and the absence of data for FICE it seems reasonable to apply the average NBI value (low confidence proportion 0.21) to the other two technologies and this is then tested in deterministic sensitivity analysis (low 0.105 to high 0.315).</td></tr>
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				NBI	Scopes (180/260)	79-100%	Rex DK. Gastroenterology 2009;136:1174–1181. Ignjatovic A, East J, Suzuki N, et al. Lancet Oncol 2009;10:1171–1178. Rastogi A, Keighley J, Singh V, et al. Am J Gastroenterol 2009;104:2422–2430.	67-80%	Denis Endoscopy 2011; 43:81–86 Ladabaum GASTROENTEROLOGY 2013;144:81–91	71.4-72.6%	Bade et al. Endoscopy 2014; 46: 172–178 Kaltenbach T, et al. Gut 2014;0:1–9.	
					190/290					80.4%	Bade et al. Endosco	

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											py 2014; 46: 172–178	
					190/290-DF	91%	Singh et al. Digestive Endoscopy 2013; 25 (Suppl. 2): 16–20			85.1%	Kaltenbach T, et al. Gut 2014;0:1–9.	
				i-Scan				81.1%	Bouwens et al. World J Gastroenterol. 2013 Jul 21;19(27):4334-43.			
				FICE		68.5%	Repici et al. Gastrointest Endosc. 2016 Sep;84(3):479-486.e3					

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<tr><td>Olympus</td><td>6</td><td>7</td><td>Executive Summary</td><td>The correct surveillance intervals for each technology have increased substantially from the previous draft report (see table below) but it is unclear why, given all the other outcomes reported in table 42 of the original report (p145) and table 47 of the current report (p169) are identical. Clarification should be provided within the report to account for this discrepancy and increase transparency.

<table>
<tr><th>TECHNOLOGY</th><th>PREVIOUS REPORT</th><th>CURRENT REPORT</th></tr>
<tr><td>NBI</td><td>87%</td><td>95%</td></tr>
<tr><td>FICE</td><td>83%</td><td>94%</td></tr>
<tr><td>I-SCAN</td><td>93%</td><td>97%</td></tr>
</table>
</td><td>The only change to the decision tree model that has been made for the current report is the surveillance intervals. All of the other clinical outcomes remain the same. The surveillance intervals have only changed slightly from the previous report:

<table>
<tr><th>TECHNOLOGY</th><th>PREVIOUS REPORT Table 42</th><th>CURRENT REPORT Table 47</th></tr>
<tr><td>NBI</td><td>95.1%</td><td>95%</td></tr>
<tr><td>FICE</td><td>90.2%</td><td>94%</td></tr>
<tr><td>I-SCAN</td><td>97.8%</td><td>97%</td></tr>
</table>

The surveillance intervals quoted by Olympus in the table (i.e. 87%, 83% and 93%) are from the text of the previous draft report and were incorrect in the text. The text of the revised report was corrected to match the new surveillance intervals in Table 47. Please accept our apologies for this error.</td></tr>
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