NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities

Diagnostics Consultation Document – Comments received during consultation from August to September 2017

Diagnostics Advisory Committee date: 26 September 2017

THEME: Changes in the care pathway

Comment number	Name and organisation	Section number	Comment	NICE response
1	DYSIS Medical Limited	2 2.4 2.10 5 5.2	**<u>Changes to the Cervical Screening Pathway</u>** a) ***"Since the publication of the original guidance there have been changes to the care pathway" (page 4)*** ***b) "…HPV Triage was rolled out across England in 2014…" (page 32)*** ***c) "…had been substantial changes to the care pathways since NICE's first diagnostics assessment of the DYSIS colposcope with DYSISmap in 2012" (page 32)*** This is incorrect. HPV triage was rolled out in 2011-12. See NHSCSP "Good Practice Guide No 3 (June 2011) – HPV Triage and Test of Cure Implementation Guide". http://www.csp.nhs.uk/files/F000198_F000196_NHSCSP%20Good%20Practice%20Guide%20no%203%20HPV%20implementation%20guidance.pdf The HPV Triage pathway was already considered in the previous NICE assessment of adjunctive technologies for colposcopy (Wade et al, 2013).	Thank you for your comment which the committee considered. Section 5.2 of the guidance has been amended to state that HPV triage was fully implemented across England in 2014. The committee noted that HPV primary screening is operational in areas included in the HPV primary screening pilot, with full roll-out expected within the 3 year review cycle for this piece of guidance.

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			The only difference between the current care pathways compared to the previous assessment is the Test of Cure protocol, which was not considered in the previous NICE assessment, however, this only affects a small fraction of the colposcopy population. ***d) "HPV primary screening has now been adopted as the standard of care in several sites in England where it was piloted" (Page 7)*** This is inaccurate. Over 95% of women in England are still being screened under HPV triage pathway. Only a small minority of women in England are having HPV testing as their primary screening test. Of the 3,225,898 women screened in 2015/16 (KC65 data), only 145,266 (~4.5%) women underwent Primary HPV screening. (Source: [redacted], Public Health England). HPV primary screening has not been fully adopted as the standard of care at the six at pilot sites. The latest available PHE figures below, show that only 36% of women across the 6 pilot sites are having HPV screening as the primary test.	Section 2.10 of the guidance has been amended to state that, at the time of writing, full roll out of HPV primary screening is expected by 2019.

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<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>Only one of the pilot sites (Manchester) has progressed towards primary HPV Screening for half of their referral population (51%).

Figures for the six Primary HPV screening pilot sites are as follows:
<table><tr><th>Pilot Laboratory</th><th>Total samples 2015-16 (25 to 64, GP and NHS CC)</th><th>Primary HPV testing 2015-16</th></tr><tr><td>Sheffield</td><td>80005</td><td>31544</td></tr><tr><td>Manchester</td><td>102154</td><td>52530</td></tr><tr><td>Liverpool</td><td>39324</td><td>14082</td></tr><tr><td>Norfolk and Norwich</td><td>50469</td><td>10912</td></tr><tr><td>Northwick Park</td><td>66601</td><td>17496</td></tr><tr><td>Southmead, Bristol</td><td>59822</td><td>18702</td></tr></table>
Source: [redacted], Public Health England

Full Primary HPV Screening roll out across England will be at the earliest, towards the end of 2019 / early 2020. See confirmation from [redacted], Public Health England: https://phescreening.blog.gov.uk/2017/01/31/deciding-how-best-to-roll-out-hpv-testing-as-the-primary-cervical-screening-test/#comment-2589.</td><td></td></tr>
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2	NHS Professional	2&5	The recommendation makes a number of wide reaching statements regarding then NHSCSP that are incorrect: HPV Triage was actually rolled out in 2011-2012 and was available at the time of the last NICE review. 'Failed test of cure' is in fact the only new group of patients. The recommendation draws a number of conclusions from HPV primary screening. At present this is only used in a very small number of patients nationally, and in less than 50% of patients in the 6 sentinel sites. I am aware of many of the discussions and issues around implementation of Primary HPV screening. Along with many in the NHSCSP I feel that the suggested national adoption date of 2019 is very 'aspirational' given the many unanswered questions regarding tendering and provision of cytology services.	Thank you for your comment which the committee considered. Section 5.2 of the guidance has been amended to state that HPV triage was fully implemented across England in 2014. Section 2.10 of the guidance has been amended to state that, at the time of writing, full roll out of HPV primary screening is expected by 2019.
3	NHS Professional	General	Discussions relating to the change in the care pathway since 2012 with the expected introduction of primary HPV testing is misleading. Colposcopy clinics will still receive cases with high grade cytology as well as low grade cytology that are HR HPV positive. The studies of DySIS and the improved sensitivity are in this group of cases and there is no evidence to suggest that the diagnostic performance will be any different in this same group of cases after primary HPV testing. There will be an additional group referred to colposcopy clinics which will	Thank you for your comment which the committee considered. The committee noted that the prevalence of disease may be different in populations referred from a HPV primary screening

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			be the HR HPV positive cases who are cytology negative. It is true that this is an untested group of cases and further research/audit will need to be carried out in this group. However to state that DySIS should not be used in the previously described cases where there is evidence of benefit and cost effectiveness because there will in the future be an additional group of cases referred is not based on sound judgement. Reality is there is also very little data to confidently know what the performance of standard colposcopy will be in the latter group either.	pathway, and recommended that further research was needed that captured the impacts of the new care pathway (see section 6.1 of the guidance document).

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THEME: Level of evidence since DG4

Comment number	Name and organisation	Section number	Comment	NICE response
4	NHS Professional	General	The 2012 NICE guidance document concluded "DySIS is a clinically and cost-effective option, compared with standard colposcopy, for examining the uterine cervix in women referred for colposcopy, and should be considered in procurement plans for colposcopy equipment". Since 2012 there is more published and presented evidence for DySIS colposcopy showing similar diagnostic capabilities to the previous reports referenced in the 2012 document. These recent evidence strengthen the initial evidence and provide greater assurances that DySIS colposcopy has improved sensitivity for the detection of HG CIN compared to standard colposcopy particularly in women with low grade cytology.	Thank you for your comment which the committee considered. The committee noted that the studies included in the external assessment group's systematic review were diagnostic accuracy studies that were judged to be at risk of bias (see section 5.3 of the guidance document). The committee reviewed additional data from the IMPROVE-COLPO study which was submitted during consultation and decided to change its provisional recommendation for the DYSIS colposcope with DYSISmap.
5	NHS Professional	General	It is inconsistent and raises serious concerns regards the process undertaken by NICE to recommend that DySIS technology is clinically and cost effective in 2012 and to then say when the	Thank you for your comment which the committee considered.

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			evidence is stronger that there is insufficient evidence to recommend it's use in 2017.	NICE diagnostics guidance is reviewed 3 years after publication to identify any relevant new evidence and any changes to the diagnostic or care pathway which may have a material effect on the published guidance. This process is set out in an interim addendum to the NICE Diagnostics Assessment Programme (DAP) manual. The review of DG4, which was subject to a public consultation, identified changes to the care pathway which were being implemented by the NHS Cervical Screening Programme – an update to the guidance was therefore considered the most appropriate course of action for this guidance. Details of the review decision for DG4 can be found on the NICE website.

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THEME: Generalisability of data

Comment number	Name and organisation	Section number	Comment	NICE response
6	DYSIS Medical Limited	5 5.4	**<u>Positive Predictive Value (PPV) and relevance of DYSIS studies</u>** **a) "the quality assurance measures for colposcopy carried out elsewhere were different to those in the UK, and that this was likely to influence the accuracy of colposcopy." (page 33)** Although each country has its own quality measures, there is no evidence that these affect the actual clinical performance of colposcopy. Notice that most quality measures around colposcopy in the UK are on procedures and processes, rather than clinical performance. The only measure on the performance of colposcopy is the PPV, which is a poor measure of diagnostic performance, as it depends on the population seen (Eusebi 2013) and can be easily "gamed". As an example, the Netherlands have a well-structured and attended screening program, colposcopy is performed by gynaecologists trained and specialised in colposcopy, and there is a quality assurance program.	Thank you for your comment which the committee considered. Section 5.4 of the guidance document notes that the committee heard from specialist committee members that quality assurance measures for colposcopy carried out elsewhere were different to those in the UK, and that this was likely to influence the accuracy of colposcopy. This section also notes that the committee considered that PPV was likely to be influenced by several confounding factors. Further, the committee heard that differences in screening programmes can impact on disease prevalence, and consequently the predictive values of a colposcopic examination.

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			b) "It further noted that the NHSCSP recommends that a satisfactory colposcopy should have a 65% positive predictive value for CIN 2+. The committee considered that although the measure of positive predictive value was likely to be influenced by several confounding factors, video colposcopy in the DYSIS studies did not achieve this benchmark, with a pooled positive predictive value of 55.78%." (page 33) In discussing the relevance of the international DYSIS studies, the comparison against the NHSCSP standard of 65% for PPV is used to show that video colposcopy with DYSIS is inferior to colposcopy in the UK. PPV is a poor, and one-sided, measure of diagnostic performance, and it is heavily affected by prevalence of disease, which depends on the population seen by the colposcopist being measured (Eusebi 2013). The PPV in the NHSCSP QA programme of 65%, is a *benchmark* and not actual performance. Data from individual colposcopists in the UK suggest that several fails to meet this benchmark, as in this example from Sheffield Teaching Hospital. (e.g. Tidy et al 2016): • Sheffield Teaching Hospital Colposcopist A: PPV = 93.4%	The committee concluded that accuracy data from non-UK studies may not be generalisable to the NHS and decided not to change the guidance document.

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			• Sheffield Teaching Hospital Colposcopist B: PPV = 54.9% • Sheffield Teaching Hospital Colposcopist C: PPV = 42.9% • Sheffield Teaching Hospital Colposcopist D: PPV = 35.0% As another example, in a primary HPV screening setting, where the prevalence of disease is lower (Palmer et al 2016) **the PPV for CIN2+ was 47%.** The pooled PPV calculation for video colposcopy with DYSIS includes the Coronado study (2016), that reported a PPV of 49%, but the population in that study included proportionally fewer HG referrals (13% compared to an average of 20% for England in NHS Cervical Screening Programme in England in 2015-16 – (KC65 data), which may explain the lower PPV. This comparison is unbalanced and the conclusion that the results of these studies are not applicable to the UK is unfounded. If it is considered necessary, comparison of PPV's should be done for patient sub-groups (LG vs HG referrals) separately.	
7	NHS Professional	2&5	The recommendation also makes comment to studies that are performed outside the UK.	Thank you for your comment which the committee considered.

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			The HPV disease process results in changes to the cervix that are colposcopically recognisable irrespective of the country in which the colposcopy takes place.	The committee considered that because of differences in colposcopy practice between countries, such as variation in quality assurance measures and screening programmes, accuracy data from non-UK studies may not be generalisable to the NHS (section 5.4 of the guidance document).
8	NHS Professional	General	There are repeated references to PPV. It's a statistical effect that using the same test in a population with higher prevalence increases the positive predictive value and vice versa. This really is quite basic statistics. So when the NHSCSP recommends that a colposcopists PPV should be 65% it is understood that this would be in a standard colposcopy clinic with an expected mix of low and high grade referrals. Most of the DySIS studies have been carried out in a cohort with a disproportionately high number of low grade cytology cases. It is inevitable that the PPV will be below 65%. The analyses and comments and discussions and conclusions relating to 1) performance of colposcopy by the colposcopists within the study showing a low PPV as being sub-standard due to the low PPV is professionally insulting and close to defamation. I would recommend removing all of it	Thank you for your comment which the committee considered. The committee considered that because of differences in colposcopy practice between countries, such as variation in quality assurance measures and screening programmes, accuracy data from non-UK studies may not be generalisable to the NHS (section 5.4 of the guidance document). The committee also

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			immediately. 2) criticising and doubting the legitimacy of the results of benefit of DySIS compared to standard colposcopy on the basis of a PPV that is below 65% is completely incorrect and a reflection of inadequate understanding on the part of the NICE panel and their investigators. 3) similar comments relating to the lower than expected sensitivity of standard colposcopy in the studies should also be removed. The sensitivities described are the actual sensitivities that can be expected and have been confirmed in repeated publications including many studies on low grade cytology not investigating adjuvant technologies. The panel are mistaken in believing that the sensitivity of standard colposcopy in low grade smears is high. The evidence clearly states that the sensitivity is low in this group of cases.	noted that PPV was likely to be influenced by several confounding factors.
9	NHS Professional	General	There are a number of comments in the document which claim that studies from non-UK countries should be considered with caution as they do not have the same quality assurance measures. This is elitist snobbery to make such claims. The studies published come from reputable clinicians and departments with a strong track record for research, publications and colposcopy. The studies have been published in peer reviewed journals and are part of the evidence base. Unless there is clear justification within the methodology or the text of the manuscripts to raise such cautions then I would recommend all such comments be removed from the document.	Thank you for your comment which the committee considered. Section 5.4 of the guidance document notes that the committee considered that variation in colposcopy practice between countries, such as the use of different quality assurance measures, means that accuracy

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				data from non-UK studies may not be generalisable to the NHS. The committee concluded that this does not suggest that performance of colposcopy in non-UK countries is worse than the UK, rather that performance may be different.
10	Zilico Limited	4.4	We are surprised by the last sentence of the section that says. "Concerns about generalisability of the results of the ZedScan studies were highlighted because the studies were ***done in a centre*** where the ***colposcopists were highly experienced*** in using the technology". The Tidy 2013 study was across ***three*** centres, Sheffield, Manchester, and Dublin. Only Professor John Tidy had been involved in the development of ZedScan and all the other investigators had never used the prototype prior to the trial. The more recent Tidy paper (Tidy et al in press)) presents data from clinical users who have been routinely using ZedScan since 2014 when their hospital decided to adopt the device routinely, but have never been involved in any development. These users went through the usual training required to adopt new medical devices and are only now experienced users of ZedScan. The statement that the studies were carried out in one centre is factually wrong and we do not understand how the EAG can make a judgement	Thank you for your comment which the committee considered. The committee decided to change section 4.4 of the guidance document to state that most of the participants in the studies were examined in a single centre.

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			about the experience that the colposcopists had had with ZedScan from the publications. If the EAG still feels it necessary to question the generalisability of the ZedScan studies, we request that the statement is at least factually correct and does not include speculation as to the experience of the users.	

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THEME: Reproducibility of adjunctive technologies

Comment number	Name and organisation	Section number	Comment	NICE response
11	DYSIS Medical Limited	5 5.5	***a) "no data on the reproducibility of the tests had been presented for the assessment" (page 33)*** Considering the nature of the colposcopic examination, reproducibility data on the patient level, that would involve multiple repeat examinations on the same patient, and numerous patients, to achieve statistical significance, are unethical to achieve. Reproducibility of results is supported by the number of different clinical studies in different settings that confirm the significant improvement in detection of CIN2+.	Thank you for your comment which the committee considered. The committee considered that no data were available to validate claims that the technologies improve the repeatability of a colposcopy examination.
12	Zilico Limited	5.5	This section refers to the lack of data on reproducibility and at the meeting of 27th July the question of the data on accuracy was also raised. We can provide the following information on the performance of ZedScan. **Accuracy** The specified accuracy for the measurement of impedance by ZedScan is +/- 2%, although this is relaxed to +/-5% at some frequencies and impedances. For the impedance spectra that correspond to HGCIN it is the +/- 2% accuracy of measurement that is relevant. ZedScan uses spectral templates to identify the cervical tissue types. The template that corresponds to HGCIN has a maximum of 250 Ohms at 76Hz and a	Thank you for your comment which the committee considered. The committee noted that section 5.5 of the guidance summarises its considerations about the lack of data on intra- and inter-observer variability when using the adjunctive technologies. The committee heard from the EAG that the data provided in the

Comment number	Name and organisation	Section number	Comment	NICE response
			minimum of 130 Ohms at 625kHz. The difference between the HGCIN template and the templates corresponding to other cervical tissues, such as normal squamous epithelium (1276 Ohms at 76Hz and 131 Ohms at 625kHz) and columnar tissue (151 Ohms at 76Hz and 115 Ohms at 625kHz) are quite large and much greater than the requirement of +/- 2% accuracy for the impedance measurements. **Reproducibility** Measurements made using the ZedScan electrode assembly on saline, with corresponding resistances between 200 and 1300 Ohms over the frequency range 152Hz to 156kHz, gave a standard deviation of 2.5% on the measurements. (Zilico internal document 'Equivalence testing_V4 BHB'). Ideally reproducibility measurements would be made by making a series of in-vivo ZedScan measurements over several days on several women. These measurements would have to include biopsy proven measurements made on both normal and abnormal cervical tissues. However, it is not ethically acceptable to make such measurements. As a consequence we have to look at the consistency of the clinical performance of ZedScan used as an adjunct to colposcopy. The recent publication on the use of ZedScan as an adjunct on over 1200 patients (Tidy et al reference 103 in DAP35) presented sensitivity and specificity figures that are consistent with the ROC curve shown in Figure 3 of reference 94 in DAP35.	consultation comment do not fully address these concerns.

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13	DYSIS Medical Limited	5 5.4 5.8 5.9	***c) "the sensitivity estimates for video colposcopy obtained in the DYSIS studies were lower than would be expected for binocular colposcopy in the NHS." (page 35)*** There is no evidence of what the true sensitivity of colposcopy is in UK NHS practice. This is not and cannot be measured in the NHSCSP, as it would require multiple biopsies or excisional treatment for all patients referred, which is unethical. <u>Please provide evidence of what sensitivity is "expected" to be, or remove the statement.</u> There is no evidence that the performance of video colposcopy is inferior to binocular colposcopy. The evidence suggests that colposcopic assessment based on images achieves similar diagnostic accuracy as live colposcopy. (Ferris et al. 2002). ***d) "They also noted that the Zedscan I study, which was done in the UK and used binocular colposcopy, reported a higher sensitivity for colposcopy." (p. 33)***	Thank you for your comment which the committee considered. The committee heard from the EAG that the true sensitivity/specificity of colposcopy in the UK is unknown, because random biopsies are generally not taken in UK studies. This impacts the conclusions that can be drawn on the incremental sensitivity/specificity of the technologies in the UK. Points c) and e) refer to advice from specialist committee members. Section 5.9 in the updated guidance (section 5.8 in the consultation document) has been amended to further clarify that these statements are committee opinion. Section 4.4 of the guidance discusses quality assessment of the included ZedScan studies; it notes that both included studies were considered at

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			e) ***"the estimates for the sensitivity of binocular colposcopy in the Zedscan studies were higher, and more representative of NHS practice, but that the estimates used in the cost-effectiveness model for colposcopy alone were taken from the meta-analyses of DYSIS colposcopy. Therefore, the committee concluded that the relative benefits of the adjunctive colposcopy technologies could have been overestimated in the modelling." (page 35)*** There is no evidence that the sensitivity for baseline colposcopy reported in the Zedscan studies is representative of UK / NHS practice. As noted in the review, these studies suffer from verification bias, so inevitably the sensitivity values are overcalled. The Zedscan study also suffers from: • Non-consecutive patient enrolment; • An elevated number of high-grade referrals (there were 48.5% HG Referrals in the study, when the average HG referral rate at Sheffield is in line with the national average of approximately 20%.)	high risk of bias by the external assessment group, of which the main source was verification bias. The committee considered the studies cited in the stakeholder's comment and noted that these studies had been included in the EAG's report.

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			• The colposcopies were performed by an experienced, expert colposcopist. The sensitivity of baseline colposcopy is comparable to that reported by Coronado et al. (2016) (73%) where a single, experienced colposcopist performed all colposcopies with DYSIS. The Cervical Screening Wales Annual Report 2015/16 (http://www.cervicalscreeningwales.wales.nhs.uk/statistical-reports) suggests that sensitivity across Wales was 67%. This was routine care and was thus achieved with no control (adjunct or random biopsies) and 85% of patients with "normal" colposcopy were not biopsied, so the underlying verification bias is likely to be significant and the true value of sensitivity closer to the pooled estimate from the DYSIS studies than that reported in the Zedscan studies. There is further evidence from studies in UK clinics that documents a low sensitivity for colposcopy (note the data below also include results from control groups seen with binocular colposcopy): • Natsis et al (2016), studied LG Referrals seen at N.G.O.C., Queen Elizabeth Hospital in Gateshead.	

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			• They used a control group of 948 women (i.e. women not examined with DYSIS) and found a 36% sensitivity (86% of these women had biopsy); • In the DYSIS group (287 women) sensitivity was 27% without the DYSISmap, and 82% with the DYSISmap; • There was a drop in the number of biopsies taken in the DYSIS group compared to the controls • Founta et al (2017), studied LG referrals seen at Taunton. • They used a control group of 390 women to compare to results with 83 women seen with DYSIS over the same period. • They found that the biopsy rate with DYSIS was lower, but CIN2+ and CIN3+ detection was higher. • The sensitivity of standard (binocular) colposcopy for CIN2+ was 21% in the control group and 26.1% in the DYSIS group (pre-DYSISmap). • Budithi et al (2017), analysed results from 393 women examined across five clinics in Wales with DYSIS and showed a 51% baseline sensitivity for all referrals, and 27% for LG referrals.	

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14	DYSIS Medical Limited	4 4.17	**Test of Cure Study (Founta)** a) ***"The accuracy of colposcopy is substantially different in this study compared with the summary estimates provided in the meta-analyses for all colposcopy referrals." (page 18/19)*** The failed Test-of-Cure population is a significantly different population, which explains the difference in accuracy. No previous data on performance of colposcopy in this high-risk population exist.	Thank you for your comment which the committee considered.
15	Zilico Limited	4.43 & 4.49	These sections, and indeed elsewhere in DAP35, report that specificity is reduced compared with colposcopy when either DYSIS or ZedScan are used as an adjunct to colposcopy. This conclusion is heavily dependent on the diagnostic accuracy figures used for the performance of colposcopy alone. DAP35 gives the wide range of published figures for the diagnostic accuracy of colposcopy (see Tables 1, 2 and 3 and sections 4.11, 4.12). A significant reason for the wide range of published figures is the different ways in which a positive test result for colposcopy is recorded. For example, DAP35 in section 2.12 page 7 quotes the England colposcopy statistics where, of the 188,179 women referred for colposcopy 61% had a treatment or procedure at their first visit. This suggests a test positive outcome of at least 61%. However, in	Thank you for your comment which the committee considered. The committee heard from the EAG that the considerable variation in diagnostic accuracy estimates for colposcopy in the identified studies means that the true diagnostic accuracy of the technologies in the UK is uncertain. Section 4.32 in the diagnostics consultation document (section 4.35 in the updated guidance)

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			sections 4.11 and 4.12 page 17 the test positive rate for colposcopy alone in the DYSIS studies is quoted as 13.77% to 42.68% and for ZedScan 41.84% or 73.47%, depending on the method of reporting. These figures are clearly neither consistent with each other nor with the English statistics and so make comparisons very difficult. In view of this we suggest that a statement should be included in the report, perhaps in the section that deals with 'Sensitivity analyses', as follows: 'Where comparisons are made between the diagnostic accuracy of the adjunctive technologies and colposcopy alone the conclusions are very dependent on the diagnostic accuracy figures for colposcopy alone that are used in the model'	describes the accuracy estimates used in modelling for the adjunctive technologies and colposcopy alone; including the source for these figures. Uncertainty about the estimates of diagnostic accuracy for the adjunctive technologies used in modelling was investigated by the EAG through sensitivity analyses; described in the diagnostics consultation document in sections 4.46 and 4.47 (now sections 4.49 and 4.50 in the updated guidance document). The committee noted that there was considerable diversity in accuracy estimates for colposcopy alone in both the DYSIS and ZedScan studies, but that the available estimated suggested that the technologies were more sensitive but less specific than

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Comment number	Name and organisation	Section number	Comment	NICE response
				colposcopy alone (section 5.6 of the guidance document).
16	BSCCP		There needs to further benchmarking of the baseline colposcopy performance in NHS setting as there is clear disagreement between dysis and zedscan studies potentially biasing results. These studies should be done outwith company studies	Thank you for your comment which the committee considered.

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Diagnostics Consultation Document – Comments received during consultation from August to September 2017

Diagnostics Advisory Committee date: 26 September 2017

THEME: Sensitivity of DYSIS

Comment number	Name and organisation	Section number	Comment	NICE response
17	DYSIS Medical Limited	General	Additionally, we would like to bring to your attention two papers presenting results from the IMPROVE-COLPO study of DYSIS (previously only available as congress posters/abstracts) have in the meantime been accepted for publication following a peer-review process, and are attached to this response (notice they are "Academic in confidence" at this stage). The IMPROVE clinical trial is the largest ever study into colposcopy with over 7,500 patients enrolled and constitutes a thorough examination into the performance of DYSIS in comparison to colposcopy performed on standard (optical) colposcopes. We request that these data are taken into consideration by the committee because they contain material evidence that challenge some of the statements in to the report and the subsequent draft recommendation. The first paper (Cholkeri-Singh et al, 2017) includes two of the largest ever cohorts in colposcopy studies (a total of 3645 women with LG referral), and compares the outcomes achieved with DYSIS used in routine practice, to a control group (colposcopy with standard methods). It finds that with DYSIS, with the same proportion of women undergoing biopsy and only a small increase in the average number of biopsies taken overall (increasing from 1 to 1.2 biopsies per patient), the detection of women with CIN2+ and CIN3+ increased by 31% and 56% respectively, which resulted from better targeted biopsies as a consequence of using the DYSISmap.	Thank you for your comment which the committee considered. The committee considered additional data provided in the pre-publication manuscripts. Section 5.7 of the updated guidance document has been amended to capture committee discussion of these manuscripts.

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			The second paper (DeNardis et al, 2017) analyses results from a cohort of 881 women (mixed referrals) examined with DYSIS in routine practice, to study the incremental benefit of biopsies selected with the help of the DSI DYSISmap after standard assessment (with biopsy selection) was completed. It finds that the additional disease that is detected is statistically significant and clinically relevant, as it is observed also at CIN3+ and for women that are at the highest risk (>30 years old). It is noteworthy that these results are not affected by verification bias nor subject to bias by using video colposcopy in the comparative arms. Whilst the IMPROVE study was conducted in the United States of America, and although there are material differences in cervical screening pathways, it is critical to note that the practice of colposcopy (as undertaken in the IMPROVE trial) is substantially equivalent to that performed in the United Kingdom.	
18	DYSIS Medical Limited	5 5.11	***a) "It heard from clinical experts that technologies which improve the negative predictive value of colposcopy may become more important after HPV primary screening is fully rolled out and people with HR HPV positive / cytology-negative results are referred for colposcopy" (Page 37)***	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			This is true, and supports the clinical value of adjunctive technologies that improve the NPV of colposcopy. HPV primary screening is expected to significantly increase referrals (>60%) to colposcopy and decrease the prevalence of disease, and is expected to have a negative impact on the performance of colposcopy (Palmer et al 2016).	
19	NHS Professional	General	The comments on verification bias are over-stated. All the studies had verification bias because no cases underwent an excisional procedure as the gold standard. It is not possible to do a study on DySIS without there being verification bias. To discard the study or minimise it's conclusions because of verification bias is excessive. Whilst the true sensitivity will never be absolutely known this is to some degree an academic discussion. The relevance of the studies are that they determined the outcomes following DySIS compared to the current standard which is bilocular colposcopy.	Thank you for your comment which the committee considered. Section 4.4 of the diagnostic consultation document noted that the main source of bias in the identified studies was verification bias, which arose because biopsies were not taken to confirm the absence of disease when the colposcopist did not identify any abnormalities. The document also notes that this is not

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Comment number	Name and organisation	Section number	Comment	NICE response
				generally considered to be good clinical practice. The committee also noted, in section 4.7 of the diagnostics consultation document, that sensitivity analysis done by the EAG designed to explore verification bias in people with negative DYSIS and colposcopy examinations suggested that sensitivity and specificity estimates decline as the number of random biopsies taken increases.

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THEME: Specificity of DYSIS

Comment number	Name and organisation	Section number	Comment	NICE response
20	DYSIS Medical Limited	4 4.14 4.43 5 5.6 5.10 5.14	**<u>Lower Specificity - Unnecessary Biopsies and Treatment</u>** ***a) "they also have reduced specificity and result in more unnecessary diagnostic biopsies and treatments (except in 'watchful waiting' clinics)." (page 29)*** ***b) "this would be at the expense of a higher false positive rate with more people having unnecessary diagnostic biopsies and treatment" (Page 34)*** Colposcopically directed punch biopsy is routinely used by colposcopists, however, techniques, number of biopsies taken, and rationale for performing a biopsy vary greatly between individual colposcopists (Myriokefalitaki et al 2016). Although in a statistical analysis, a lower specificity may be correlated with higher rates of biopsy, real world data from UK DYSIS studies (Natsis et al 2016, Founta et al 2017, Budithi et al 2017) and from KC65 data at clinics using DYSIS, suggest that there is **<u>no</u>** increase in biopsy rates after the routine adoption of DYSIS. (**See Table 1**)	Thank you for your comment which the committee considered. Section 5.7 of the updated guidance has been amended to capture the committee discussion of the additional data provided. The committee noted that the real world outcome data provided suggest that adoption of DYSIS does not increase biopsy rate. The committee concluded that despite methodological limitations of these data, they provide reassurance that the increase in biopsies implied by the results of the diagnostic accuracy studies alone may not be realised in practice in

Comment number	Name and organisation	Section number	Comment	NICE response
			Furthermore, the IMPROVE-COLPO study that compared colposcopy outcomes with DYSIS to a control group using standard colposcopes, showed there was no increase in the number of patients undergoing biopsy, only a small increase in the number of biopsies taken with DYSIS (one biopsy in five patients with low-grade referral), (Cholkeri-Singh et al 2017), with a resulting benefit in detection that was proportionally higher, detecting 31.4% more women with CIN2+ and 56% more with CIN3+, suggesting that biopsies are more efficient (i.e. better targeted) with DYSIS. ***c) "The committee considered whether this data could be studied to see if biopsy and detection rates of CIN 2+ had increased in centres that had already adopted DYSIS colposcopy with DYSISmap". (page 38)*** This data is available *(**see** **Table 1** at the bottom of this response)* and demonstrates that the adoption of DYSIS did not drive an increase in biopsy rates. Hospitals listed have been using DYSIS routinely for over 2 years. We have also shown the national average and the biopsy rate for Sheffield Teaching Hospital (Zedscan).	centres using DYSIS colposcopy with DYSISmap.

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THEME: Specificity of DYSIS

Comment number	Name and organisation	Section number	Comment	NICE response
			Even if a drop in specificity does result in additional biopsies, this will not affect costs, as typically all biopsies are placed in the same specimen pot and are processed together, and thus do not incur additional costs. A false positive indication by the DYSISmap will **never** be used to drive a LLETZ treatment that would otherwise not be performed, therefore the statement that its use will result in unnecessary treatments is incorrect. In clinical practice, in a See and Treat scenario, the DYSIS map is used predominantly to avoid over-treatment, by picking out patients who do not have obvious/large HG lesions, and who may benefit from having a diagnostic biopsy performed over treatment at the first visit. **Table 1** The table below, built from KC65 data (NHS Cervical Screening Programme in England in 2012-13 to 2015-16), demonstrates that there is no observable increase in the biopsy rate at NHS hospitals using DYSIS for more than two years. The year highlighted in blue indicates the first year of DYSIS use at each hospital. For reference, we added Sheffield Teaching Hospital (Jessop) (using Zedscan) and the average for All England.	

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THEME: Specificity of DYSIS

<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>NHS Trust</th><th>DYSIS Installation</th><th colspan="4">KC65 Biopsy Rate Data -Table 26b</th></tr>
<tr><td></td><td></td><td>12/13</td><td>13/14</td><td>14/15</td><td>15/16</td></tr>
<tr><td>Queen Elizabeth Hospital, Gateshead</td><td>2013/14</td><td>55.90%</td><td>60.00%</td><td>54.80%</td><td>57.40%</td></tr>
<tr><td>Barnsley General Hospital</td><td>2013/14</td><td>17.00%</td><td>19.40%</td><td>22.70%</td><td>19.20%</td></tr>
<tr><td>Princess Royal Univ. Hosp. (Kings)</td><td>2014/15</td><td>n/a</td><td>66.90%</td><td>60.70%</td><td>60.50%</td></tr>
<tr><td>Bedford Hospital</td><td>2015</td><td>27.00%</td><td>18.00%</td><td>23.70%</td><td>22.80%</td></tr>
<tr><td>Southend Univ. Hospital</td><td>2014/15</td><td>68.80%</td><td>71.80%</td><td>61.50%</td><td>52.60%</td></tr>
</table>
</td><td></td></tr>
</table>

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THEME: Specificity of DYSIS

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			Nottingham NHS Treatment Centre (Circle)	2015	n/a	44.20%	37.80%	32.70%	
			Stepping Hill Hospital, Stockport	2015	64.70%	58.60%	50.20%	35.80%	
			Medway Hospital, Kent	2015	30.00%	35.60%	39.70%	37.70%	
			North Devon Hospital, Barnstaple	2015	20.10%	16.20%	29.80%	29.50%	
			Sheffield Teaching		55.80%	55.40%	46.50%	42.00%	

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THEME: Specificity of DYSIS

<table>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Hospital (Jessop)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>All England average</td><td></td><td>49.00%</td><td>48.20%</td><td>47.70%</td><td>47.00%</td></tr>
</table>
</td><td></td></tr>
<tr><td>21</td><td>NHS Professional</td><td>1 Recommendation 1.1</td><td>My NHS unit has fully integrated DYSIS into our colposcopy clinics since the start of 2015. Similar to other units that use DYSIS consistently, we have seen no increase in biopsy rate, but a significant increase in our detection rate of CIN in those biopsies that are taken. I presented my own units 24-month data in the opening lecture of the 2017 BSSCP annual conference.</td><td>Thank you for your comment which the committee considered.</td></tr>
<tr><td>22</td><td>NHS Professional</td><td>General</td><td>There seems to be further confusion in relation to the reduced specificity of DySIS. Specificity is defined as the ability of a test to correctly identify those without the condition. It is accepted that the specificity is lower with DySIS colposcopy. The clinical effect of this however depends on what an individual colposcopists practice is in the absence of a significant lesion. If the usual practice when they see a lesion but which they do not think is HG CIN is to biopsy it anyway the clinical effect of DySIS which may suggest that it could be HG CIN is zero in that a biopsy would have been taken anyway. If the usual clinical practice is not to take a biopsy</td><td>Thank you for your comment which the committee considered.

The results of the economic model suggest that if the adjunctive technologies have a lower specificity than colposcopy alone this could</td></tr>
</table>

			than this will result in more biopsies. NHSCSP however recommends that a biopsy should be taken so the clinical effect of DySIS in effect is to encourage the colposcopist to conform to NHSCSP guidelines. In a second scenario where after standard colposcopy there is no lesion to biopsy at all it also depends on what the colposcopists usual practice is. Some colposcopists take a random biopsy of the SCJ and some take no biopsy at all. If DySIS shows a lesion in the same case which it considers may be HG CIN then a biopsy will be taken. The comparison in this group is a DySIS directed biopsy after DySIS colposcopy or a random biopsy or no biopsy at all. It is in these cases that the increased sensitivity of DySIS detects the additional cases of HG CIN. In some colposcopists practice it will result in more biopsies to achieve the greater sensitivity and in other colposcopists practices it will not. The greater sensitivity will have been achieved through a better directed biopsy. The studies included in fact have shown that there were no increase in biopsies for the reasons stated. It is also incorrect to assume that more biopsies will increase the cost as when more than one biopsy is taken from a case all biopsies are submitted in the same single specimen pot. Also, it is incorrect to state that the reduced specificity will result in more unnecessary treatments. There is no evidence to support this and it is not in keeping with standard colposcopy practice or be considered in the decision making process. Whilst the document concentrates heavily on the increased number of biopsies it actually is recommended in many national and international guidelines that multiple biopsies should be taken rather than single	be associated with an increase in unnecessary biopsies and treatments (section 5.10 in the original consultation document). This section (section 5.11 in the updated guidance) has been amended to take account of additional real world data provided at consultation regarding increases in biopsy rate as a result of adopting the DYSIS technology (as discussed in the response to comment 20 above).

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THEME: Specificity of DYSIS

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			biopsies as there is good evidence already that the sensitivity improves with multiple biopsies.	

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THEME: Accuracy of ZedScan

Comment number	Name and organisation	Section number	Comment	NICE response
23	Zilico Limited	4.9	The last sentence of this section says that 'but when a regression model was fitted to Tidy et al. (2013), statistical significance was not reached (difference in log diagnostic accuracy 0.488, p=0.078)'. We are surprised at this statement, that conflicts with our own statistical analysis. However, DAP35 Evaluation Report page 114 does give some background to this statement and states that 'These results suggest that ZedScan may have better diagnostic accuracy than colposcopy alone'. and then: 'Fitting a logistic regression model to the data from the prototype study found that the improvement in diagnostic accuracy was not **quite** (word not included in section 4.9) statistically significant (difference in log diagnostic accuracy: 0.488, SE 0.28. p-value 0.078)'. Logistic regression analysis is commonly used for a meta-analysis of many studies but not usually applied to a single set of data (see Simmonds MC and Higgins JPT, A general framework for the use of logistic regression models in meta-analysis, Statistical Methods in Medical Research, 25(6), 2858-2877, 2016). Logistic regression makes no assumptions about the distribution of points about the regression and as such, whilst this is appropriate for a meta-analysis, it will tend to increase the SE and hence increase the calculated p-value when applied to a single study. As a consequence, we would suggest	Thank you for your comment which the committee considered. Section 4.9 of the updated guidance has been updated to state that when a regression model was fitted to Tidy et al. (2013), the improvement in diagnostic accuracy was not quite statistically significant (difference in log diagnostic accuracy 0.488, p=0.078). This is to match wording used in the diagnostics assessment report as noted in the consultation comment. The committee heard from the external assessment group that they had adopted a conservative approach for this analysis because of the limited data available.

Comment number	Name and organisation	Section number	Comment	NICE response
			that it is not appropriate to include the statement contained in the final three lines of section 4.9; i.e. please remove the following text. *But when a regression model was fitted to Tidy et al. (2013), statistical significance was not reached (difference in log diagnostic accuracy 0.488, p=0.078).*	
24	Zilico Limited	4.43 & 4.49	PLEASE NOTE: FOR CLARIFICATION AFTER THE 27th JULY MEETING As mentioned above there are two main methodologies to measure the performance of colposcopy. This is also as observed in other publications in the literature; for example Cantor et al Accuracy of colposcopy in the diagnostic setting compared with the screening setting. Obstet Gynecol 2008; 111:7-14. Zilico chose to use the disease present (DP) methodology to implement within ZedScan as this is accepted as a better reflection of true clinical practice. The DP method provides a high sensitivity. In order to provide better specificity ZedScan further stratifies patients, dependant on referral cytology/referral HPV test. The table below summarises the cut-offs incorporated in ZedScan and how these relate to the two different methodologies of measuring colposcopic performance. The correct comparator between colposcopy and ZedScan+colposcopy for the DP methodology is the performance described in table 3 (cut-off 0.768) reference 94.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that in the economic model, the performances of colposcopy alone, DYSIS and ZedScan I are assessed in the same way: the probability of being diagnosed as CIN2+ given patient's true health state. Further, current national guidelines were used to inform treatment practice in the

<table>
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<tr><td></td><td></td><td></td><td>Zilico introduced a specific cut-off using the ROC curve from the BJOG 2013 paper for ‘see-treat’ patients to ensure that ZedScan meets the required standard as specified by the NHSCSP #20 for a 90%+ PPV. This cut-off ensures a specificity of 95%+. Whilst the sensitivity for these patients drops to 65%, the patients not identified for immediate treatment will then be selected for biopsy with a 92% sensitivity for detection of High Grade disease.
<table>
<tr><th></th><th>+ve/-ve colposcopic impression (CI)</th><th>Incorporated in ZedScan</th><th>Equivalent cut-off in BJOG 2013 Table 3</th><th>Equivalent cut-off in BJOG 2013 Table 2</th><th></th></tr>
<tr><td>Low-grade referrals</td><td>+ve CI</td><td>High level threshold</td><td>0.768</td><td>1.321</td><td></td></tr>
<tr><td></td><td>-ve CI</td><td>Higher level threshold</td><td>0.768</td><td>1.321</td><td></td></tr>
<tr><td>High-grade referrals</td><td>+ve CI</td><td>Lower level threshold</td><td>0.768</td><td>1.321</td><td></td></tr>
<tr><td></td><td>-ve CI</td><td>Low level threshold</td><td>0.768</td><td>1.321</td><td></td></tr>
</table></td><td>economic model. In particular two structural assumptions were made to model the diagnostic and treatment pathways. Firstly, people were only treated at first examination (in a ‘see and treat’ clinic) if a colposcopy result is positive (CIN 2 or worse) and cytology indicates a high grade lesion. The second structural assumption in the model is that patients with a high grade cytology referral were assumed to undergo diagnostic biopsy if they have a negative colposcopy.

The use of different thresholds by the ZedScan I in a ‘see and treat clinic’ and any possible impact of ZedScan I in identifying patients for discharge without a diagnostic biopsy are therefore not</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Name and organisation</th><th>Section number</th><th>Comment</th><th>NICE response</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>See & Treat</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>High-grade referrals</td><td>+ve CI (see & treat)</td><td>Specific High level threshold for HG referrals</td><td>n/a</td><td>n/a</td><td>Provides a 95% specificity</td></tr>
</table>

It was commented at the meeting that DySIS only supplied one methodology to assess performance i.e. Colposcopic Impression (CI) and not the DP method. Therefore DySIS has only been assessed using the CI method. If CI method has to be used then the correct performance against standard colposcopy for the UK is presented in Table 2 of reference 94. This data is also supported by the Marel paper (van der Marel J, van Baars R, Quint WGV, Berkhof J, del Pino M, Torne A, et al. The impact of human papillomavirus genotype on colposcopic appearance: a cross-sectional analysis. BJOG. 2014; 121: 1117–1126.) rather than the data from Louwers or other non-UK settings.

If we are using CI methodology then the correct comparator performance for ZedScan +Colposcopy is the data from table 2 (cut-off 1.321), reference 94. This shows that sensitivity is unchanged but specificity is higher.</td><td>modelled. The main impact of ZedScan I in the economic evaluation is from the higher proportion of patients with CIN2+ detected with ZedScan I compared to colposcopy alone, as reported in Tidy (in press).

The committee noted that Tidy et al. (2013) - reference 94 in the diagnostics assessment report - reports accuracy data from a prototype device, rather than the ZedScan I (as discussed in section 4.9 of the consultation document).</td></tr>
</table>

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THEME: Accuracy of ZedScan

Comment number	Name and organisation	Section number	Comment	NICE response
			Please note that the NHS cervical screening programme uses the DP method to assess the PPV and APV of cytology, table 19a, of the National Statistic Bulletin (http://content.digital.nhs.uk/catalogue/PUB18932/nhs-cervical-stat-eng-2014-15-data-tabl.xlsx) and so DP is an appropriate measure but when PPV of referral to colposcopy is assessed by the national programme the CI method is used.	
25	Zilico Limited	3.6 & 4.9	EIS as technology enables the use of different cut-offs to provide better diagnostic accuracy as described in Tidy 2013. ZedScan I incorporates different cut-offs (which cannot be changed by the user) such that it ensures the best possible diagnostic test accuracy for every woman examined taking into account the reason for referral. For example, a high-grade referral patient with a visual indication of high-grade CIN might be considered suitable for see & treat but this can be influenced by the ZedScan results. The algorithm applies a higher cut-off to this patient's data such that the specificity and corresponding PPV for a positive result are above the 90% threshold as set by the NHSCSP 20; this provides the user with additional data to either proceed with immediate treatment or to revert to a diagnostic biopsy. If there are no readings above this cut-off a lower cut-off is applied to the data and any readings that are above this will be indicated to the user who can decide to take a diagnostic biopsy. Overall this combination of cut-offs provides a corresponding sensitivity of 92% for the detection of high-grade disease.	Thank you for your comment which the committee considered. Further detail has been added to section 4.9 to clarify that the threshold used is set by the manufacturer.

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Comment number	Name and organisation	Section number	Comment	NICE response
			For a patient with a low grade referral, where a clinician is seeking reassurance that there is no disease the cut-off applied is such that there is a high NPV. We are concerned that in Section 4.9 the phrase "depending on the threshold used" suggests that a user of ZedScan can change the cut-off. This is incorrect. The cut-off can only be changed by the manufacturer and the cut-offs applied have been chosen to achieve the best clinically relevant diagnostic accuracy test as described above. We suggest that the phrase 'depending on the threshold used' should be removed.	

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THEME: Clinical significance of additional disease detected

Comment number	Name and organisation	Section number	Comment	NICE response
26	DYSIS Medical Limited	5 5.4 5.8 5.9	**<u>Concerns about the increased Sensitivity</u>** ***a) "It heard from clinical experts that the additional high-grade lesions (CIN2+) detected using the adjunctive colposcopy technologies, could in fact be low-volume disease, which could regress without treatment." (page 35)*** There is no evidence that the additional disease detected with the use of DYSIS is regressive CIN2+ or clinically irrelevant. All analyses of the additionally detected disease done at the level of CIN3+ (Louwers et al. 2015, DeNardis et al. 2017, Cholkeri-Singh et al. 2017) find that detection is increased also at that threshold, and suggest that the additional lesions are clinically important. The global standard (and NHSCSP Guidelines / Publication 20) is that CIN2+ lesions should be removed, except for women who are pregnant. In some circumstances for CIN2 lesions on younger women or women that have not completed their family, clinicians may choose to conservatively manage, in case the CIN2 spontaneously regresses and cytology returns to normal (but would be treated if persistent for two years).	Thank you for your comment which the committee considered. The committee noted evidence provided in the Cholkeri-Singh et al. (2017) and DeNardis et al. (2017), which were both submitted to the committee as pre‑publication manuscripts during consultation, which indicates that DYSIS detects additional cases of CIN3 compared to standard colposcopy. Section 5.15 has been amended to state that further data had been provided at consultation that showed that DYSIS was able detect additional CIN3 lesions compared to standard colposcopy. The committee therefore concluded that there was sufficient evidence that DYSIS is able to detect additional clinically

Comment number	Name and organisation	Section number	Comment	NICE response
			Zaal et al (2012) showed that with DYSIS the sensitivity to detect patients with CIN2+ among those infected by high risk HPV-16, the most carcinogenic sub-type, was very high, confirming that the results are clinically important. The objective of DYSIS is not to drive more women into treatment, but to ensure that every colposcopist is accurately informed on the condition of every patient. Armed with the correct information, the colposcopist is then able to make an informed decision – rather than hope that any missed CIN2 will regress. If a patient has a low volume CIN2 lesion on biopsy, the management decision is in the hands of clinician to either: 1. Treat with LLETZ loop excision (Biopsy is histologically confirmed as HG-CIN, so within NHSCSP guidelines) 2. Conservatively manage, giving the lesion the opportunity to regress with planned future cytology and follow-up colposcopy. ***b) "Anecdotal evidence suggested that some clinicians were now using use either ablative techniques or 'watchful***	important lesions to recommend its continued adoption. Section 5.10 of the guidance has been amended to acknowledge the BSCCP survey.

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Comment number	Name and organisation	Section number	Comment	NICE response
			waiting' management strategies for low-volume CIN 2 in some circumstances" (Page 35/36) This is not anecdotal. The BSCCP conducted a full survey of all accredited colposcopists in 2015 and found that >50% of them practice conservative management (Macdonald et al, 2015). The potential benefit for these women from the standardisation of colposcopy, the use of objective measures and the use of features such as side-by-side, dynamic comparison of images from follow-up examinations that DYSIS offers, should be included in the discussion.	
27	DYSIS Medical Limited	4 4.8 4.19	***a) "There was no clear evidence that DYSIS improved the detection of cervical cancer." (page 14)*** ***b) "There were insufficient data to determine whether the increase detection of CIN 2 was associated with a reduction in cervical cancer." (page 19)*** The NHS cervical screening program is not intended to detect cervical cancer, but to **prevent** cervical cancer by detecting and treating premalignant lesions, and the role of the adjunctive technologies is to assist colposcopists in their assessment.	Thank you for your comment which the committee considered. Sections 4.8 and 4.22 of the document report outcome data that were looked for, but not found, in the systematic review done by the external assessment group. Reporting their absence is important, because it resulted in assumptions being made about progression rates from CIN to invasive cancer in the

Comment number	Name and organisation	Section number	Comment	NICE response
			It is virtually impossible to perform a study of meaningful power on the detection of cervical cancer, as its incidence is rare and that any study to assess differences in cervical cancer detection arising from undetected CIN2 or CIN3 that is allowed to progress, would be unethical. The statements above must be removed or edited to reflect this. The World Health Organisation comment that cervical cancer is one of the world's deadliest *but most easily preventable* forms of cancer for women, responsible for more than 270,000 deaths annually, 85% of which occur in developing countries. However, there is evidence (Livingston et al 2016) that the use of DYSIS does help identify cervical cancers that fall outside of typical templates (e.g. distant from the transformation zone or colposcopically small lesion size) and could be missed at colposcopy.	cost effectiveness model. Whilst this was not reported in the included studies, the impact of treating CIN2+ and preventing progression to invasive cancer is modelled in the economic analysis.
28	DYSIS Medical Limited	5 5.11	***b) "The committee concluded that it was uncertain whether the adjunctive colposcopy technologies would increase detection of disease that would progress to cancer if not treated. Therefore, the cost savings in the model could not be considered robust." (page 37)***	Thank you for your comment which the committee considered. The committee noted continuing uncertainty over whether additional

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Comment number	Name and organisation	Section number	Comment	NICE response
			As discussed above (see comment #6), it is unethical (and practically impossible) to study the progression of lesions to cancer. The purpose of the screening system is to prevent cancer by removing CIN before it has the chance to progress to cancer, and the adjunctive technologies improve colposcopy towards this aim. It can therefore not be expected that they provide proof that the disease they detect, if left alone, would/could have progressed to cancer. The World Health Organisation now regards cervical cancer as a completely preventable disease, if a woman undergoes regular screening. Please amend the report to clarify this.	CIN2 lesions detected by the adjunctive colposcopy technologies would increase detection of disease that would progress to cancer if not treated because of the absence of data on the natural history of low volume CIN2 disease. The committee therefore recommended that further data are collected (see research recommendation 6.4) to help understand whether small volume CIN2, which in some circumstances may be managed with watchful waiting, may regress.
29	NHS Professional	General	The CROWN initiative is a means of standardising clinically relevant outcomes in research studies. It is accepted that for diagnostic tests for cervical cancer prevention the clinically relevant outcome is HG CIN including CIN2 and CIN3. The current document appears to be confused in it's understanding of what the clinically relevant outcome measure is.	Thank you for your comment which the committee considered. The diagnostics consultation document does not suggest that CIN3 can be safely left or not treated. Any recommendations on managing lesions detected at

			1) It argues for and against the inclusion of CIN2 when there are no published data that safely recommends non-treatment. Whilst there is increasing practice of regular surveillance it is unclear what the clinical outcome of this practice will be in the absence of any national or clinical recommendations of what the surveillance strategy should be during the period of conservative management. Whilst it mentions small CIN2 lesions in young women, the questions are how small, how young, what if they had a high grade cytology, previous cervical history, how many biopsies were taken, was it just one and therefore was CIN3 likely to be present but missed. Due to these many uncertainties relating to CIN2 it is inappropriate to not include CIN2 as an outcome measure when assessing the diagnostic performance of DySIS. Regardless of these comments all of the publications show an increased sensitivity for the detection of CIN3 as well as CIN2. 2) It is wholly unjustified and unacceptable and clinically dangerous to claim that there are types of CIN3 that can either be left untreated or can be safely missed. There is no evidence to support this at all! The document should not include comments that cannot be justified in the absence of evidence to support it. It has been tested in law and found to be unethical and in keeping with medical malpractice resulting in sentencing and imprisonment. All such comments or inferences should be removed from the document unless adequate justification for their inclusion can be made. The onus is on the sceptics to prove that CIN3 that is missed by standard colposcopy but detected by DySIS is not of clinical relevance. Until such evidence is	colposcopy are outside the scope of this guidance. Section 5.10 has been amended to further clarify that the committee heard from clinical experts that the additional high-grade lesions detected using the adjunctive colposcopy technologies could in fact be low-volume CIN 2 disease which could regress without treatment. The committee further heard that data on the natural history of low-volume CIN2 is not available, and that some clinicians were now using use either ablative techniques or 'watchful waiting' management strategies for low-volume CIN 2 in some circumstances.

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Comment number	Name and organisation	Section number	Comment	NICE response
			available all CIN3 should be considered clinically relevant and any assumptions made regards this point should not be included in a professional document.	

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THEME: Adverse effects of treatment

Comment number	Name and organisation	Section number	Comment	NICE response
30	NHS Professional	DAP Comments P19	With regard to premature delivery I would suggest that further consideration is given to assessing the impact of this with specific respect to gestation. There is a huge body of evidence on perinatal mortality and morbidity with respect to gestational age of delivery. In essence there is only marginal, if any change in perinatal mortality and morbidity beyond 34 weeks, especially if corticosteroids have been administered. The modelling does not take this into account.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that QALYs and costs associated with premature delivery used in modelling were from a reference that used a threshold of less than 37 weeks to define preterm birth. The excess risk of preterm birth used in modelling, derived from Kyrgiou (2016), was therefore based on the same definition of prematurity (<37 weeks). The committee noted that the EAG had carried out a scenario analysis in which adverse obstetric outcomes were removed from the model; and that the results of the model did not change substantially in this analysis (reported in the diagnostics consultation document sections 4.47 and 4.48).

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THEME: Adverse effects of treatment

Comment number	Name and organisation	Section number	Comment	NICE response
31	NHS Professional	General	The detrimental effect of excisional treatments on future pregnancies has only been identified in cases where the depth of treatment was greater than 10mm or when multiple treatments were carried out.	Thank you for your comment which the committee considered.

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THEME: Economic modelling

Comment number	Name and organisation	Section number	Comment	NICE response
32	DYSIS Medical Limited	4 4.36	***a) "DYSIS: £9.24" (page 26)*** As mentioned in our previous feedback, this price includes the cost of the DYSIS Viewer which is a software that is not used at the time of colposcopy and is thus irrelevant. The corrected cost was noted as £8.55, but was only included in a scenario sub-analysis.	Thank you for your comment which the committee considered. Section 4.39 reports the costs used in the base case of the economic model. The committee noted that the EAG had considered £9.24 as the most appropriate cost per patient to use for DYSIS. In addition, the committee further noted that, as highlighted in the stakeholder's comment, a sensitivity analysis had been carried out to explore the effect of parameter uncertainty on the costs of technologies. This sensitivity analysis did not result in substantial changes to the results of the cost effectiveness analysis (as reported in sections 4.49 and 4.51 of the diagnostics consultation document).

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THEME: Economic modelling

Comment number	Name and organisation	Section number	Comment	NICE response
33	DYSIS Medical Limited	4 4.40	***a) "The probability of a positive colposcopy result was: identical for people with clear, HPV or CIN 1 result identical for people with CIN 2 or 3 or invasive cancer." (page 27)*** This is inaccurate and will overestimate the performance of colposcopy. Colposcopy performs better (higher sensitivity and higher PPV) among women referred with high-grade cytology compared to low-grade cytology and higher grades of disease (Hopman et al 1998, Louwers et al 2015). ***b) "Examinations with DYSIS or Zedscan I were equivalent in duration to a standard colposcopy examination" (page 28)*** This is incorrect, as using Zedscan adds at least 2-3 minutes to the examination, 20% of a standard colposcopy appointment, or a total of two appointments' time over a typical colposcopy list in a NHS clinic.	Thank you for your comment which the committee considered. The committee noted that the quotations included in the stakeholder comment were assumptions made in the base-case economic modelling analysis (as set out in section 4.40 of the diagnostics consultation document). The committee heard from the external assessment group that assumption a) was needed in the economic model because studies used a CIN2+ cut-off to report sensitivity and specificity. The committee noted that the external assessment group had explored the impact of this assumption in a sensitivity analysis using unpublished data provided by DYSIS manufacturer where sensitivity and specificity are reported for different cut-offs (CIN1, CIN2/3 and cancer). The committee

Comment number	Name and organisation	Section number	Comment	NICE response
				further noted that this sensitivity analysis did not change the model results substantially (as reported in the diagnostics consultation document sections 4.49 and 4.51). The committee also heard from clinical experts that they do not think there is a substantial difference in the length of time taken per examination with the DYSIS and ZedScan technologies.
34	DYSIS Medical Limited	4 4.44	a) ***"time horizon restricted to 1 screening interval (3 years)" (page 29)*** We do not understand the rationale for this scenario analysis, as the outcomes are obvious.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that the rationale for using a time horizon of three years in this scenario analysis was to identify the main drivers of cost and benefits in the short term, taking into account the

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				complexity of the modelled care pathways.
35	Zilico Limited	5.4 & 5.8	We are surprised bearing in mind the committee's conclusion why non-UK data was used in the EAG's model when considering performance. We believe UK colposcopy data should be used in spite of the theoretical verification bias as this is more relevant to UK colposcopy practice.	Thank you for your comment which the committee considered.

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36	DYSIS Medical Limited	General	DYSIS is committed to developing and driving new technology that improves outcomes for women in the UK, in the fight to eradicate cervical cancer, as well as improving education for women, resulting in a better understanding of their condition. The recommendation as it stands today, would likely make it difficult for many women to access this advanced technology, leaving colposcopy as the continued weak link in the cervical cancer pathway.	Thank you for your comment which the committee considered.
37	Zilico Limited	1.1	Whilst we agree with the underlying thrust of the document that new technologies should be assessed before adoption, we are concerned that the second bullet point at the end of this section indicates that any colposcopy services that are not currently using an adjunctive technology should **only** (emphasis added) use them as part of a research study. Given that elsewhere in the document (e.g. sections 1.1, 4.42, 5.1) there are clear statements that adjunctive technologies dominate conventional colposcopy, i.e. are more effective and cost less, and no significant contraindications are raised, we are surprised that NHS Trusts should be discouraged from gaining these benefits without first carrying out a research study. We believe that it is more appropriate to encourage the use of local service evaluations prior to adopting a new technology. Indeed, there are advantages in having new medical device technologies assessed in this	Thank you for your comment which the committee considered. The recommendations for further research are intended to inform future updates of this guidance. NICE diagnostics guidance is reviewed 3 years after publication to identify any relevant new evidence which may have a material effect on the published guidance. This process is set out in an interim addendum to the NICE Diagnostics

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			way as local variations in population and practice can be taken into account. The fact that the data are produced in a routine setting can be more compelling and relevant to clinicians as compared with a tightly-controlled, and therefore artificial, clinical study. Our experience to date strongly suggests that, for medical devices especially, NHS clinicians and procurement professionals place a greater emphasis on real-world data from the use of new products than from clinical trial data. This emphasis is different from pharmaceuticals.	Assessment Programme (DAP) manual.
38	Zilico Limited	1.1	We would suggest that the wording of the second bullet point in section 1.1 is changed as follows: • Colposcopy services not currently using the technologies should consider conducting research or a service evaluation prior to adopting them in routine practice.	Thank you for your comment which the committee considered.
39	NHS Professional	1 Recommendation 1.1	I am very surprised and dismayed by the draft recommendation for DYSIS, especially given that DYSIS is now being routinely used in an ever increasing number of clinics within the UK and DYSIS does not appear to have a limited current evidence base.	Thank you for your comment which the committee considered.

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			The suggestion that DYSIS should be used to gather more evidence or only as part of a research trial would most likely result in the denial of any further women access to the technology, and its many benefits	
40	NHS Professional	1 Recommendation 1.1	The recommendation also takes no account of the many significant additional Quality Assurance improvements that the DYSIS archiving system provides. These relate to being able to review the whole colposcopy of any previous visit, either with or without the adjunctive map. This is crucial in MDT discussions of any patient, and in the robust management of the ever-increasing number of patients who are opting for conservative management of CIN2.	Thank you for your comment which the committee considered. The committee discussed the potential benefits of being able to record images of the cervix during a colposcopy, and heard that this can be particularly important if a lesion is being monitored over time. It further heard from clinical experts that increasingly colposcopes are being used with monitors.
41	BSCCP		Further to my previous comments, I think the statement that the adjuncts to colposxcopy should only be used in a research setting is too strong. I think if colposcopy units have invested in the dysis colposcope or Zedscan then these technologies have been demonstrated to improve diagnostic performance it should always be left to individual units / colposcopists to make a decision on which colposcopes they use.	Thank you for your comment which the committee considered.

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			From a NHS screening perspective and prevention of invasive disease, there needs to be more evidence on whether these new technologies make colposcopy practice more efficient and more cost effective	
42	NHS Professional	General	Page 1 asks via public consultation whether 1) the summaries are reasonable interpretations of the evidence: NO THEY ARE NOT, SEE COMMENTS BELOW 2) are the recommendations sound: NO THEY ARE NOT, SEE COMMENTS BELOW 3) are they suitable for the NHS: NO THEY ARE NOT, SEE COMMENTS BELOW 4) equality of opportunity: NO IT DOES NOT, SEE COMMENTS BELOW 5) eliminating unlawful discrimination: NO IT DOES NOT, SEE COMMENTS BELOW 6) fostering good relations between people: NO IT DOES NOT, SEE COMMENTS BELOW	Thank you for your comment which the committee considered.

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43	NHS Professional	General	Accepting that the evidence can always be improved upon, it is coflicting and illogical to recommend that one can use the DySIS colposcope on NHS patients if they have already purchased it but one cannot use it on NHS patients if they have not purchased one but are considering doing so. Either 1) it is recommended based on evidence of benefit/reduced cost or 2) it is not recommended because of evidence of harm/increased cost or 3) there is insufficient evidence when no recommendations can be made. It cannot be a mixture of the three where we were told there was evidence of benefit so we can use it and then when the evidence is stronger in favour of benefit to say the evidence is not sufficient so one cannot use it when there is no evidence showing harm or increased cost. The quality of evidence should be graded. Based on the presence of at least one peer reviewed medline published controlled study without randomisation this would be classed as graded level IIA evidence. Grade B recommendations can therefore be made that DySIS colposcopy has improved clinical and cost effectiveness compared to standard colposcopy.	Thank you for your comment which the committee considered. The use of the GRADE classification system is not covered by the NICE diagnostics assessment programme manual, and is not currently part of its methods.

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Comment number	Name and organisation	Section number	Comment	NICE response
44	Zilico Limited	1.1	In addition, the setting up and conduct of a research study comes with a greater burden (both costs, time and complexity) on the local NHS resources which would, if made a requirement, act as a barrier to the adoption of new technologies. We also believe that service evaluations can provide most of the additional information mentioned in section 6 'Draft recommendations for further research'. Methods to measure the impact of adjunctive technology on both decision making (section 6.2) and the patient experience (section 6.3) can be incorporated into a service evaluation. The question of the natural history of low-volume CIN (section 6.4) is best addressed through the NHSCSP Research Advisory Committee. Section 6.1 recommends that further studies should be done to establish the clinical significance of the additional HG CIN lesions detected by adjunctive technologies. This could be incorporated into a service evaluation except for the issue of verification bias. Taking diagnostic biopsies from patients who have no evidence of disease is discouraged within the screening programme (NHSCSP 20 3rd edition March 2016 section 6.6) and the morbidity associated with these biopsies would come with little to no benefit for the individual, making it difficult to justify on ethical grounds. This is particularly true given that the localised nature of	Thank you for your comment which the committee considered. Recommendation 6.1 states that studies that assess clinical outcome data should be designed to minimise verification bias. The committee did not consider that it would be unethical to carry out such studies, depending on the study design and reference standard chosen.

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			most lesions means that taking a single biopsy will not provide definitive evidence of disease; taking multiple biopsies or even carrying out a loop excision would clearly be impractical and unethical.	

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THEME: General comments and factual accuracy

Comment number	Name and organisation	Section number	Comment	NICE response
45	DYSIS Medical Limited	General	We are disappointed with the change in the draft recommendation from the previous 2012 NICE review. We surmise, that the committee have made this draft recommendation based on 3 critical points of discussion: 1) That substantial changes in the care pathway have been implemented since the previous recommendation. 2) That the body of evidence supporting the efficacy of DYSIS colposcopy is insufficient to support the continued recommendation by NICE for the wider adoption of DYSIS. 3) That much of the clinical evidence supporting DYSIS' efficacy was not conducted in the UK NHS cervical screening setting. We are challenging these points in the table below, using evidential proof and would request that a further review of the evidence is required.	Thank you for your comment which the committee considered.
46	DYSIS Medical Limited	1	***"…colposcopy services not currently using the technologies should only use them as part of a research study" (page 2)*** This draft recommendation for DYSIS, and the change from the previous recommendation, is based on the arguments that:	Thank you for your comment which the committee considered.

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Comment number	Name and organisation	Section number	Comment	NICE response
			1) That substantial changes in the care pathway have been implemented since the previous recomme dation. 2) That the body of evidence supporting the efficacy of DYSIS colposcopy is insufficient to support the continued recommendation by NICE for the wider adoption of DYSIS. 3) That much of the clinical evidence supporting DYSIS' efficacy was not conducted in the UK NHS cervical screening setting. We provide evidence to support that: 1) There have been little or no changes in the pathways since the previous assessment. 2) The evidence for DYSIS is substantial, and larger than in 2012 (as recognised by the EAG in their independent assessment), and is now both investigational and translational in a standard NHS colposcopy setting. The body of evidence incudes: 11 peer reviewed articles, 63 congress abstracts (including >25 oral presentations) 3) In addition to the growing, real-world translational evidence, originating from various hospitals in the UK (DYSIS is routinely	

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			used at 30+ NHS hospitals), the international evidence for DYSIS originates from countries with comparable overall patient demographics and efficiency in preventing cervical cancer, and is therefore relevant to UK practice. Below we outline the arguments and sources of evidence that challenge the summary position and many of the statements in the Diagnostics Consultation Document.	
47	DYSIS Medical Limited	4 4.18	***a) "Two DYSIS studies reported no adverse events." (page 19)*** Please correct this (see previous response). Also note that the recently accepted articles from the IMPROVE-COLPO study (Cholkeri-Singh et al 2017, DeNardis et al 2017), also report that there were no adverse events.	Thank you for your comment which the committee considered. The committee heard from the external assessment group that comment is correct and three DYSIS studies reported no adverse events. Section 4.21 of the guidance has been amended to reflect this.
48	DYSIS Medical Limited	4 4.22	***a) "the number of respondents per questionnaire was not reported" (page 22)***	Thank you for your comment which the committee considered. Section 4.25 of the guidance has been amended to clarify that the number of

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			These numbers were provided in the feedback to the original EAG report; they were 433 and 330 respectively.	respondents per questionnaire was not reported in the conference abstract available to the external assessment group.
49	DYSIS Medical Limited	4 4.24	a) ***"68 patients and 45 colposcopists responded" (page 22)*** This is not correct. It was 45 colposcopist questionnaires, not 45 colposcopists. The number of the different colposcopists that completed questionnaires was not reported.	Thank you for your comment which the committee considered. Section 4.27 of the guidance has been amended to clarify that 45 colposcopist responses were received (number of colposcopists unknown).
50	DYSIS Medical Limited	4 4.25	a) ***"This found that correct diagnosis was more frequent with DYSIS than with conventional colposcopy for colposcopists with low and medium levels of experience. There was no difference for highly experienced colposcopists." (page 21)*** This statement is misleading and should be clarified. The said conclusion was not made for the dichotomous classification of cases between "Normal/low-grade" vs "high-grade" as in all other studies and analyses included, but was trichotomous (Normal vs low-grade vs high-grade).	Thank you for your comment which the committee considered. The committee heard from the external assessment group that this statement was based on a distinction between four possible diagnoses (as reported in external assessment group report 4.5.3.2): normal/metaplasia, low-grade,

Comment number	Name and organisation	Section number	Comment	NICE response
			Table 2 of that paper (Coronado et al 2014) shows that the inclusion of the DYSIS map improved the detection of CIN2+ significantly for colposcopists of all experience levels, including those with high experience (p=0.001).	high-grade and cancer and reflects the findings presented in Coronado (2014). It further heard from the EAG that they agreed that table 2 in this study suggests that the inclusion of the DYSIS map improved the detection of CIN2+ significantly for colposcopists of all experience levels. However this finding should be interpreted with caution as it is based on a small subgroup analysis of a retrospective review of images projected to colposcopists rather than on actual "live" examinations conducted in a colposcopy clinic. Section 4.28 of the diagnostics guidance has been amended to reflect this.
51	DYSIS Medical Limited	4 4.41	***a) "when the results of any diagnostic biopsies were available" (page 28)***	Thank you for your comment which the committee considered. Section 4.44 of the guidance has been amended to clarify that in the base-

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			This statement suggests that treatment could be performed also when the results were negative. Consider changing to *"when the results of any diagnostic biopsies were positive for CIN2 or worse".*	case model, in a 'watchful waiting' clinic treatment was done at the second visit when the results of any diagnostic biopsies showed CIN2+.
52	Zilico Limited	4.18	We feel that it should be made clear that the adverse events were the consequence of the colposcopy, specifically, in the case of bleeding, to the taking of biopsies, and were unrelated to the use of the device.	Thank you for your comment which the committee considered. Section 4.21 of the guidance has been amended to state that it is uncertain whether the adverse events occurring in the ZedScan studies were related to the use of the ZedScan device.
53	Zilico Limited	4.26	For clarity we suggest that the statement "Wade et al. (2013) was produced for NICE's diagnostics guidance on adjunctive colposcopy technologies and found that DYSIS dominated colposcopy (that is, DYSIS cost less and was more effective than colposcopy)." is changed to the following: Wade et al. (2013) was produced for NICE's diagnostics guidance on adjunctive colposcopy technologies (***now fully replaced by this***	Thank you for your comment which the committee considered. This guidance is a full update of the NICE diagnostics guidance on the DYSIS colposcope with DYSISmap and the Niris Imaging System which was published in 2012. The referenced Wade et al. (2013) is the publication of the diagnostics assessment report

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			guidance) and found that DYSIS dominated colposcopy (that is, DYSIS cost less and was more effective than colposcopy).	(DAR) which was produced for the original guidance in 2012, rather than the guidance itself. The original DAR will remain published in the NIHR journal library.
54	Zilico Limited	5.4 & 5.8	We request that this key conclusion from the committee discussion should be included in the main body of the guidance document. "The committee concluded that because of differences in colposcopy practice, such as fewer quality assurance measures and the use of video colposcopy, the accuracy data from non-UK studies may not be generalisable to the NHSCSP"	Thank you for your comment which the committee considered. The committee discussion section (section 5) is part of the guidance document which will be published on the NICE website as part of the final guidance.
55	DYSIS Medical Limited	DAR comments, BSCCP P43 P44	It is not clear whether the opinions/statements in the feedback to the original assessment report represent the BSCCP (consensus statement) or are an individual opinion. If that was a consensus, please confirm how that was derived. ***"Many of the DYSIS papers are from Gateshead but I can't see a baseline colposcopy sensitivity in this setting****" (Page 43 of DAR Comments)*	Thank you for your comment which the committee considered. This refers to a comment received from an external stakeholder on the diagnostics assessment report (DAR) for this topic, rather than the diagnostics consultation document. Comments produced by external

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THEME: General comments and factual accuracy

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			There are only two studies from Gateshead (Natsis et al 2016 on LG referrals, Founta et al 2015 on Test of Cure), and both present baseline colposcopy sensitivity. Natsis et al presented sensitivity among LG referrals for a control group seen with binocular colposcope (36%). Notably: • Dr Founta received the **BSCCP Award** for best oral presentation of this work at the 2015 BSCCP congress (Nottingham) • Dr Natsis was awarded a **BSCCP Prize** for this poster at the 2016 BSCCP congress (Bradford) ***"The majority of the studies are driven by their respective industry sponsor and therefore might be biased in their outcomes**" (Page 44 of DAR Comments)* Please provide the evidence that the sponsorship of any DYSIS studies may have biased the actual outcomes published or presented by the investigators/clinicians. Without any evidence, we ask that this	stakeholders are the responsibility of the stakeholder themselves, rather than NICE. Comments received by NICE on the DAR consultation are published for transparency.

DIAGNOSTICS ASSESSMENT PROGRAMME

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities

Diagnostics Consultation Document – Comments received during consultation from August to September 2017

Diagnostics Advisory Committee date: 26 September 2017

THEME: General comments and factual accuracy

Comment number	Name and organisation	Section number	Comment	NICE response
			statement is removed from the report and the public domain as it is misleading.	
56	NHS Professional	DAP Comments P48-52	As a member of the main BSSCP Executive Committee please can you confirm as to how this opinion was achieved? At present it would potentially appear to be the opinion of one or a small number of individuals. As such it cannot represent a consensus view of the BSCCP that has a current membership of 1554 colposcopists.	Thank you for your comment which the committee considered. This refers to a comment received from an external stakeholder on the diagnostics assessment report (DAR) for this topic, rather than the diagnostics consultation document. Comments produced by external stakeholders are the responsibility of the stakeholder themselves, rather than NICE.