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 second consultation from October to November 2017

Diagnostics Advisory Committee date: 10 January 2018

THEME: Service evaluations to assess device performance

Comment number	Name and organisation	Section number	Comment	NICE response
1	Zilico Ltd.	1.3	We are disappointed to see that the draft recommendation relating to ZedScan still indicates that any new centres should *only* (emphasis added) use the device in research studies. In our response to the previous draft of the consultation document, we set out in detail our arguments for using service evaluations rather than research studies. We believe that the points made there are still valid and would appreciate a response as to why these arguments have not been accepted. In addition to setting out the original comment below we wish to add the following information. Since ZedScan's CE Mark in 2013 we estimate that ZedScan has been used on at least 6000 patients in the UK, Ireland, Germany, France, Sweden, Finland, Israel, Bahrain, and India. The following UK centres, after reviewing trial data on ZedScan, are carrying out service evaluations of the product before routine adoption. These service evaluations are carried out according to an agreed protocol (minimum 100 patients as this will be statistically significant for the improvement in performance expected for ZedScan). These real-world data are then used to make a case to adopt ZedScan at the hospital. These evaluations follow best practice ethical principles of consent, anonymity and data protection & privacy as consistent with local practice in each centre. These real-world data are being prepared for a meta analysis publication.	Thank you for your comment which the committee considered. The committee noted the ongoing research on the use of the ZedScan I and considered that this could inform a future update of this guidance. However, the committee highlighted that any subsequent research on the ZedScan I should aim to address the research recommendations and highlighted that that the methodological quality of the research will be considered in any future assessment. It considered that, depending on the design conduct and reporting standards, service evaluations may not be sufficiently robust to address the evidence gaps it had highlighted. Recommendation 1.3 in the diagnostics guidance document has been amended to specify that colposcopy services that

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			The centres in the UK that are currently (or about to begin) evaluating ZedScan within the context of their colposcopy service are listed below. **SCOTLAND** [redacted]. This study will also seek to collect both patient and colposcopist feedback on the use of ZedScan. In addition, the following centres in England are routinely using ZedScan. Royal Stoke Hospital County Hospital, Stafford	implemented the ZedScan I before this guidance was published are encouraged to contribute to studies which support the research recommendations in the 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. In addition, NICE may review and update the guidance at any time if significant new evidence becomes available. This process is set out in an interim addendum to the NICE Diagnostics Assessment Programme (DAP) manual. The committee considered the Muszynski et al. study. It noted that this study provided some additional data on the performance of the ZedScan I; but that these were not sufficient to resolve the considerable uncertainty about the accuracy and

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			St Mary's Hospital, Manchester Royal Hallamshire Hospital, Sheffield The current draft guidance raises the issue of parity of care for women across England because of the additional delay in new centres adopting ZedScan; a woman attending a clinic where ZedScan is not already in use would be denied the improved colposcopy examination available to women in clinics that use ZedScan. [redacted] The evaluation carried out at CHU d'Amiens-Picardie has been published: Muszynski C et al; J Gynecol Obstet Hum Reprod. 2017 Sep 1. pii: S2468-7847(17)30162-9. doi: 10.1016/j.jogoh.2017.08.007. [Epub ahead of print]. **The impact of using electrical impedance spectroscopy (ZedScan) on the**	clinical effectiveness of this technology. Details of the study have been added to section 4.11 of the guidance document.

Comment number	Name and organisation	Section number	Comment	NICE response
			performance of colposcopy in diagnosing high grade squamous lesions of the cervix. The key result from this study was that ZedScan with colposcopy increased the detection of high grade lesions by 47.3% (increasing the number from 19 to 27) including detecting one case of invasive cancer. Comment previously submitted. 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 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	Please also see the comments and responses from the 26 September 2017 committee meeting for a response to the following points.

Comment number	Name and organisation	Section number	Comment	NICE response
			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. 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 most lesions	

Comment number	Name and organisation	Section number	Comment	NICE response
			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. On the point about verification bias we would also point to a recent publication that investigated the effect of taking random additional biopsies from areas that did not show any aceto-whiteness (Wentzensen et al, Multiple Biopsies and Detection of Cervical Cancer Precursors at Colposcopy. J Clin Oncol 2014; **33:** 83-9). This is a large study on diagnostic colposcopy with 690 women recruited. The data presented by these authors shows that taking a single random biopsy from women who would otherwise not have been biopsied identified disease in only 3.3% of cases. This study also looked at the impact of taking a single additional biopsy from a non-aceto-white area in women who also had taken from aceto-white sites and again found only a small increase in the detection of disease (4%). These data show that whilst verification bias will over-estimate sensitivity and under-estimate specificity the effect will be small and therefore the colposcopy performance data from Tidy et al 2013 are relatively accurate. It is also worth noting that in the ZedScan case study using real clinic data, the use of the device increased the detection of high-grade disease by 13.25%, which is significantly higher than the impact of random biopsies reported by Wentzensen et al. We believe that this further supports the view that using ZedScan identifies disease that would be missed by conventional colposcopy and could not be identified by simply increasing the number of biopsies taken.	

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			We would suggest that the wording of the second bullet point in section 1.1 is changed as follows: • **Colposcopy services not currently using ZedScan should consider conducting research or a service evaluation prior to adopting it in routine practice.**	

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THEME: Sensitivity and specificity estimates

Comment number	Name and organisation	Section number	Comment	NICE response
2	Zilico Ltd.	4.35	The quality of the outputs from the model depends upon the quality of the inputs for both ZedScan and DySIS as well as the colposcopy comparator. Our concern is that there is still a lack of understanding of the difference between the Colposcopic Impression (CI) and Disease Present (DP) methods of calculating performance figures leading to a mistaken conclusion that using ZedScan leads to reduced specificity when the opposite is the case. The two methods were described in our comments on the previous draft and are also explained in Tidy et al (2013). In summary: The CI (Colposcopic Impression) method reports the outcome of Colposcopy as negative if the clinical opinion is that HGCIN is not present, even though in many cases a biopsy is still taken to exclude disease. The DP (Disease present) method reports the outcome of Colposcopy as negative if no procedure (biopsy or immediate treatment) is carried out. In the committee discussion, reference has been made to the diagnostic performance of colonoscopy. When a colonoscopy is performed the operator may believe a cancer to be present and take a biopsy. This will give a colonoscopic impression (CI) of cancer being present, however the colonoscopist will also remove for biopsy any other areas of abnormality such as adenomas or polyps, even if they do not look like a cancer. However, the decision as to whether to operate is dependent on the results of all biopsies taken and not just the part of the	Thank you for your comment which the committee considered. The committee heard from the EAG that they consider that the DP and CI methods of calculating performance figures used in the ZedScan papers results in alternative thresholds for assessing diagnostic accuracy of colposcopy, since they change what is considered to be a positive or negative result for the index test. The EAG reported results for ZedScan from both thresholds in the diagnostic assessment report but preferred to use results calculated using the CI method because it was more comparable to methods used in the DYSIS studies and enabled indirect comparisons of the two interventions. The EAG considered that the overall conclusions would not have been changed if results calculated using

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			bowel removed based on colonoscopic impression. This clinical management is based on the disease present(DP) methodology we have described. We are of the opinion that the expert colposcopists will agree that, whilst it is true that colposcopic impression (CI) is important for assessing a colposcopist's performance, for the woman being referred for a colposcopic examination the most important outcome is whether they have disease or not (DP). The expert colposcopists should be able to inform the committee as to the relevance and importance of the DP method to the clinical management of women referred to colposcopy. Whilst colposcopic impression can guide a decision to take a biopsy, relying on this alone leads to cases of HG-CIN being missed. To compensate for this colposcopists will take biopsies from areas not considered to be consistent with HG-CIN or random biopsies from the cervix (as recommended by US guidelines; ref below). The final clinical management decision is based on the result of all biopsies taken irrespective of colposcopic impression. The colposcopy experts will be able to confirm that colposcopic impression is only part of the diagnostic pathway. The outcome of a colposcopic examination is therefore based on the DP method and not colposcopic impression. The Cervical Screening Programme for England uses the DP method when calculating the performance of the programme. For example, in the Statistical Report for the Cervical Screening Programme, Appendix B – Definitions includes a	the DP method for ZedScan could have been used in the model. The EAG further explained that a structural assumption was included in the model to reflect the DP approach in clinical practice and the current colposcopy and programme management guidance. This assumption meant that all members of the modelled cohort who had a high-grade referral for colposcopy had a biopsy, regardless of the result of the colposcopy. To use the DP accuracy figures directly would require a structural change in the model and would preclude comparisons with DYSIS. The committee decided that no changes to the diagnostics guidance were needed. Diagnostic accuracy results from the Tidy et al (in press) paper, which

Comment number	Name and organisation	Section number	Comment	NICE response
			section on Achievable Standards for cervical screening and for both the PPV and APV key indicators, the Numerator takes into account all reported cases of HG disease (cancer, AIS, CIN2, CIN3) regardless of the colposcopic opinion; although the DP terminology is not used, this is identical to the DP methodology we have employed. The DP method for analysing the outcome of a referral to colposcopy is not only the most appropriate method to use, it is the only method used by the NHSCSP and hence has significant bearing on the performance of the screening programme, cost effectiveness to the NHS and, most importantly, it is the only way to measure the outcome for the woman referred to colposcopy. We are of the opinion that the expert colposcopists will be able to confirm this. The CI method is based upon what the Colposcopist thinks, whereas the DP method is based upon what they actually do. The DP method gives rise to a higher sensitivity but a lower specificity than the CI method. It is very important that the same method is used when comparing Colposcopy alone with that of adjunctive Colposcopy. Table 3 gives the model inputs for DYSIS using the CI method. This is evidenced by the high specificity (87.4%) and relatively low sensitivity (57.9%) given for Colposcopy alone. The model inputs for ZedScan 1 should use the DP method where specificity is 38.5% and sensitivity 88.5% for Colposcopy alone.	were previously academic in confidence, have now been added to the guidance document.

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			It is stated that the accuracy of ZedScan 1 was taken from Tidy et al (In press) but the figures are not given because at the time we marked them as being confidential. These should now be included and should be as follows: Sensitivity — Specificity Colposcopy alone — 88.5% (79.9% to 94.4%) — 38.5%(29.4% to 48.3%) ZedScan I — 97.9% (96.6% to 99.2%) — 58.4% (55.1% to 62.1%) These use the DP method and show an increase in BOTH Sensitivity and Specificity when ZedScan I is used as an adjunct to Colposcopy. We believe that the conclusions drawn from the model are in error because the performance figures for the comparator colposcopy are based on the CI rather than DP method. The model should be re-run using the most appropriate figures for colposcopy as this is likely to affect the overall conclusions of the report. **Reference for US Guidelines** ASCCP Colposcopy Standards: How Do We Perform Colposcopy? Implications for Establishing Standards. Waxman AG, Conageski C, Silver MI, Tedeschi C, Stier EA, Apgar B, Huh WK, Wentzensen N, Massad LS, Khan MJ, Mayeaux EJ Jr, Einstein MH, Schiffman MH, Guido RS. J Low Genit Tract Dis. 2017 Oct;21(4):235-241. doi: 10.1097/LGT.0000000000000336	

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THEME: Sensitivity and specificity estimates

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3	DYSIS Medical Ltd.	5.9	***a) "the sensitivity estimates for video colposcopy obtained in the DYSIS studies were lower than would be expected for binocular colposcopy in the NHS."*** *(page 37)* There is no evidence of what the true sensitivity of colposcopy is in routine UK NHS practice. This is not and cannot be measured in the NHSCSP, as it would require multiple/additional biopsies or excisional treatment for all patients referred, which is unethical. Please provide evidence of what sensitivity is "expected" to be, or remove the statement. 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 actually 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):	Thank you for your comment which the committee considered. Point a) refers to an opinion from clinical experts on the committee which states that there was no consensus amongst experts. The committee decided to add research considerations on the need for further studies comparing digital colposcopy systems with binocular colposcopy and for a more consistent approach to assessing the accuracy of colposcopy in future studies. Please see sections 5.19 and 5.20 of the guidance document.

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			A) Natsis et al (2016), studied LG Referrals seen at N.G.O.C., Queen Elizabeth Hospital in Gateshead. • In the control group of 948 women (i.e. women <u>not</u> examined with DYSIS) they 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 B) 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). C) 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. ***b)*** Furthermore, there is no evidence that the performance of video colposcopy is inferior to binocular colposcopy (also notice comparisons in above examples that indicate a similar performance). On the contrary, evidence suggests that	

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			colposcopic assessment based on images achieves similar diagnostic accuracy as live colposcopy. (Ferris et al. 2002)	

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THEME: Model results

<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>4</td><td>Zilico Ltd.</td><td>4.46
Table 6</td><td>Table 6 is difficult to understand and may contain errors.

Table 6 Secondary outcomes per 1,000 people referred for colposcopy
(60-year time horizon)
<table><tr><th>Clinic</th><th>Strategy</th><th>Missed CIN 2+</th><th>Cancers</th><th>LLETZ</th><th>Unnecessary LLETZ</th><th>Unnecessary diagnostic biopsy</th></tr><tr><td colspan="7">HPV triage</td></tr><tr><td rowspan="3">'See and treat'</td><td>Colposcopy</td><td>69</td><td>43</td><td>466</td><td>27</td><td>139</td></tr><tr><td>DYSIS</td><td>30</td><td>34</td><td>501</td><td>61</td><td>229</td></tr><tr><td>ZedScan I</td><td>3</td><td>29</td><td>524</td><td>82</td><td>291</td></tr><tr><td rowspan="3">'Watchful waiting'</td><td>Colposcopy</td><td>69</td><td>44</td><td>449</td><td>0</td><td>137</td></tr><tr><td>DYSIS</td><td>30</td><td>37</td><td>465</td><td>0</td><td>260</td></tr><tr><td>ZedScan I</td><td>3</td><td>32</td><td>477</td><td>0</td><td>347</td></tr><tr><td colspan="7">HPV primary screening</td></tr><tr><td rowspan="3">'See and treat'</td><td>Colposcopy</td><td>82</td><td>33</td><td>446</td><td>22</td><td>164</td></tr><tr><td>DYSIS</td><td>34</td><td>25</td><td>478</td><td>50</td><td>296</td></tr><tr><td>ZedScan I</td><td>4</td><td>20</td><td>498</td><td>68</td><td>386</td></tr><tr><td rowspan="3">'Watchful waiting'</td><td>Colposcopy</td><td>82</td><td>34</td><td>432</td><td>0</td><td>172</td></tr><tr><td>DYSIS</td><td>34</td><td>27</td><td>450</td><td>0</td><td>316</td></tr><tr><td>ZedScan I</td><td>4</td><td>22</td><td>460</td><td>0</td><td>417</td></tr><tr><td colspan="7">Abbreviations: CIN 2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papilloma virus; LLETZ, large-loop excision of the transformation zone.</td></tr></table></td><td>Thank you for your comment which the committee considered.

The committee noted that table 6 is not a snapshot of one screening cycle, and heard from the EAG that it is the sum of the occurrence of a particular event (LLETZ for instance) over the 60 cycles for the 500,000 patients simulated. The total is then reported in terms of outcomes per 1,000 people. Therefore an event can occur several times for one individual. In the case of the unnecessary LLETZ, the point raised is correct. Colposcopy, DYSIS and ZedScan eventually result in a similar number of LLETZ performed on patients with CIN2+. The EAG explained further that there is no inconsistency with the fact that</td></tr>
</table>

			We assume that the column headed 'LLETZ' relates to all such procedures carried out on the population of 1000 and that 'Unnecessary LLETZ' is the number of those procedures that did not result in the identification of HG disease (cancer, AIS, CIN2, CIN3). As a result, subtraction one from the other should produce the number of LLETZ procedures where HG disease was confirmed by histopathology. Applying this approach to the data for the 'See and Treat' clinic in the HPV Triage scenario produces the following results Colposcopy: 439 LLETZ with confirmed disease DySIS: 440 LLETZ with confirmed disease ZedScan: 442 LLETZ with confirmed disease Effectively the same number of confirmed cases of disease with all three strategies. The column 'Missed CIN2+ indicates that DySIS missed 39 fewer cases than colposcopy (30 vs 69) and ZedScan missed 66 fewer cases than colposcopy (3 vs 69). How is this possible if all strategies have the same number LLETZ with confirmed disease? The situation is similar in the HPV primary screening scenario. We also note that in the 'Watchful waiting' clinic where there are apparently no Unnecessary LLETZ the number of LLETZ procedures does not match with the numbers calculated above for 'See and Treat' but the numbers of Missed CIN2+ are identical between the two types of clinic. We would also query the figures for 'Unnecessary diagnostic biopsy', which show an increase for ZedScan over both colposcopy and DySIS, as we believe	there are differences in the number of CIN2+ cases missed. If colposcopy (or DYSIS or ZedScan) misses CIN2+, the patient can still be diagnosed and treated as CIN2+ if either i) a biopsy has been performed despite a negative colposcopy result; or ii) the patient is correctly diagnosed at a subsequent screening. Further detail has been added to section 4.47 in the guidance document and table 6.

			this is a result of using the wrong reference figures for colposcopy as described in Comment 4 above.	
5	Zilico Ltd.	4.46 Table 6	As a separate point, we do not understand how it has been possible to identify how the use of the DySIS device would impact on the performance of See & Treat. We are not aware of any publications that present relevant data. We also note that Comment 18 in the list of DAR Comments, which was submitted by an NHS Professional, states that few, if any, clinicians would perform a treatment based on the DySIS map; it is clear that this comment comes from a current DySIS user. NHSCSP 20 clearly states that See & Treat should only be carried out where the PPV for the procedure is >90% and we have presented evidence in the ZedScan Case Study that this can be achieved using ZedScan as an adjunct. In the absence of any evidence that DySIS can enable colposcopists to achieve this level of performance it seems inappropriate and unjustified to present data on how this device might perform in this type of clinic.	Thank you for your comment which the committee considered. The committee noted that the distinction between 'see and treat' and 'watchful waiting' clinics in the model is an assumption used to capture heterogeneity in treatment decisions. Further, the model assumes the same diagnostic accuracy of DYSIS in see and treat and in watchful waiting clinics. The committee noted that the sensitivity estimates (and the source of these estimates) used for DYSIS in the model were stated in the diagnostics assessment report and the guidance document (section 4.36) and decided that no changes to the diagnostics guidance were needed.

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THEME: Model results

6	Zilico Ltd.	4.52	It is stated that 'The ZedScan I results were sensitive to changes in the cost of diagnostic and treatment biopsies because of its increased sensitivity and lower specificity compared with colposcopy.'. This statement is incorrect (see comment 4). A similar statement is made in section 5.6 that ZedScan is less specific than colposcopy alone. **These statements need to be corrected. They are likely to be a consequence of the incorrect figures for the performance of Colposcopy alone being used in the model (see comment 4)**.	Thank you for your comment which the committee considered. The committee noted that the accuracy estimates used for both ZedScan I and colposcopy are stated in section 4.36 of the guidance document. Please see the response to comment number 2 above for further explanation on which estimates were selected for use in the economic model, and the assumptions made to capture current colposcopy guidance on colposcopically directed biopsies.

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THEME: Generalisability of data

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7	Zilico Ltd.	4.4	This section states that there are concerns about the generalisability of the ZedScan results because the participants were examined in a single centre. We have previously pointed out that this is erroneous and that 3 centres participated in the study and the publication itself does make it clear that this was a multi-centre clinical study. We also refer to NICE MIB 20 *The ZedScan as an adjunct to colposcopy in women with suspected cervical intra-epithelial neoplasia*; on page 23 the breakdown of the participants between the three centres is clearly set out. However, we accept that that the comment about generalisability is reasonable as comparative data between centres has not been published. As set out in comment 1 above and in our previous responses ZedScan is being evaluated in several centres in the UK and Europe. We suggest that more accurate wording would be: **Concerns about the generalisability of the results of the ZedScan studies were highlighted because, whilst Tidy et al (2013) does report on pooled data collected in two UK and one Irish centre, sufficient comparative data between many centres is not yet published.**	Thank you for your comment which the committee considered. The committee noted that this section states that "Concerns about generalisability of the results of the ZedScan studies were highlighted because *most* of the participants in the studies were examined at a single centre". The committee therefore decided that no changes to the guidance document were needed.
8	DYSIS Medical Ltd.	5.4	***"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."*** *(page 34)* 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	Thank you for your comment which the committee considered. Section 5.4 of the diagnostics guidance document notes that the committee heard from clinical experts that quality assurance measures for colposcopy

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THEME: Generalisability of data

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			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% • 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.	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. Section 5.4 of the guidance document has been amended to further clarify that the committee noted that the use of PPV values to assess the generalisability of studies to the UK is problematic.

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THEME: Generalisability of data

Comment number	Name and organisation	Section number	Comment	NICE response
			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.	

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THEME: Collection of further data as part of the KC65 dataset

Comment number	Name and organisation	Section number	Comment	NICE response
9	Public Health England	5.17	The NHS Cervical Screening Programme colposcopy clinical professional group discussed the request to include details of adjunctive technologies on the KC65 at a recent meeting. The consensus was that the KC65 is not an appropriate vehicle for this type of ad hoc research-based data collection. The purpose of the Korner returns is to monitor the performance of the screening programme and its individual services not to evaluate specific equipment or possible clinical protocols. We did consider if there were other ways in which we could support centralised data collection for this specific evaluation of adjunctive technologies. However, the resources that would be necessary for the NHS and PHE Screening to invest in order for local data systems to be amended and data collection and analysis arrangements to be set up would be prohibitive. At this time, we therefore concluded that informally encouraging individual services to ensure they collect local audit data on their use of adjunctive technologies through our established screening networks was the only viable option.	Thank you for your comment which the committee considered. The committee acknowledged that making the necessary changes to the KC65 required to collect data on the performance of the adjunctive technologies would be difficult, but wished to encourage consideration of whether the dataset could be adapted for this purpose in the future. It also suggested that, if it is not possible to use the KC65 to collect this data nationally, then local audits should be used to collect data. Section 5.18 of the guidance document has been amended to reflect this.

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THEME: Factual inaccuracies

Comment number	Name and organisation	Section number	Comment	NICE response
10	Zilico Ltd.	4.9	Our concern is the final sentence of this section. We made the case in our previous comments that the method of analysis (logistic diagnostic accuracy) was not appropriate where only one study was being analysed as this would reduce the statistical significance found. It was our understanding of the discussion that took place during the meeting of 26th September that this point was accepted but the sentence has still been included in the revised report.	Thank you for your comment which the committee considered. The committee noted that the regression model had been fitted to data from 1 study and that the EAG had described this as a conservative approach. Section 4.9 of the guidance document has been amended to reflect this.
11	DYSIS Medical Ltd.	4.17	***"in which DYSIS was used after an initial assessment with standard colposcopy to identify further sites for biopsies."*** *(page 19)* This is misleading as it suggests that the standard part of the examination was not done with DYSIS. Please edit the text, e.g. to *"A thorough colposcopic assessment with biopsy selection, using DYSIS, was completed before the DYSISmap was reviewed and used to identify further sites for biopsies."*	Thank you for your comment which the committee considered. Section 4.18 of the guidance document has been amended to clarify that the DYSISmap was used after an initial assessment with DYSIS video colposcopy to identify further sites for biopsies.
12	DYSIS Medical Ltd.	4.21	***"Three DYSIS studies reported no adverse events."*** (page 20) As mentioned in previous responses, <u>four</u> of the DYSIS studies included in the EAG review reported that there were no adverse events. The two recently published IMPROVE-COLPO articles (Cholkeri-Singh et al in press and DeNardis et al 2017) also reported the lack of any device related adverse events (in large cohorts of patients).	Thank you for your comment which the committee considered. Section 4.22 of the guidance document has been amended to specify 4 studies.

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THEME: Factual inaccuracies

Comment number	Name and organisation	Section number	Comment	NICE response
13	DYSIS Medical Ltd.	5.6	***"this could be at the expense of a higher false positive rate with more people having unnecessary diagnostic biopsies and treatment".*** *(page 35)* A higher false positive rate may lead to additional biopsies but not to unnecessary treatments. A treatment should only be performed when justified by cytology or by punch biopsy histopathology result. A false positive indication by the DYSISmap will never trigger 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 DYSISmap 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.	Thank you for your comment which the committee considered. The committee noted that the available diagnostic accuracy studies suggest that DYSIS is less specific than colposcopy alone, and that use of these estimates in the economic model showed that unnecessary treatment could potentially occur following use of the DYSIS device in see and treat clinics (see table 6 in the guidance document). The committee decided that no change to the diagnostics guidance document was needed.
14	DYSIS Medical Ltd.	*4.18*	***"reported for referrals for low-grade (CIN 1) and high-grade (CIN 2 and 3) cytology"*** *(Page 19)* The description of cytological low/high-grade as **CIN** is inaccurate and confusing, as "CIN" is used for findings of histopathology review.	Thank you for your comment which the committee considered. Reference to CIN has been removed from this section of the guidance document.
15	DYSIS Medical Ltd.	4.22	Page 20: "CIN2" needs to become "CIN2+"	Thank you for your comment which the committee considered.

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THEME: Factual inaccuracies

Comment number	Name and organisation	Section number	Comment	NICE response
				The guidance document has been amended as suggested.
16	DYSIS Medical Ltd.	4.43	Page 28, 6th bullet: "CIN2" should become "CIN2+"	Thank you for your comment which the committee considered. The guidance document has been amended as suggested.

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THEME: Requests for clarification in the guidance document

Comment number	Name and organisation	Section number	Comment	NICE response
17	DYSIS Medical Ltd.	*4.7*	***"This suggests that DYSIS increases the number of biopsies taken"*** *(page 14)* To reflect that clinical decisions are up to the clinicians, consider changing to *"A drop in specificity with the DYSISmap may lead to an increased number of biopsies taken …"*	Thank you for your comment which the committee considered. Section 4.7 of the guidance document has been amended to clarify that the cited results suggest that DYSIS increases the number of people suspected of having CIN2+, and may therefore increase the number of biopsies taken, but may not improve the ability to discriminate between lesions with and without CIN 2+ when compared with colposcopy.
18	DYSIS Medical Ltd.	4.8	***"There was no clear evidence that DYSIS improved the detection of cervical cancer"*** *(page 14)* It should be clarified that the adjunctive technologies under review are not intended to diagnose cancer, and also that the incidence of cancer is so low that this is hardly measurable in a study.	Thank you for your comment which the committee considered. This sentence has been removed from the guidance document.
19	DYSIS Medical Ltd.	4.8	***"There was no clear evidence that DYSIS improved the detection of cervical cancer"*** *(page 14)* This statement also applies to Zedscan I, so should be included in the relevant paragraph.	Thank you for your comment which the committee considered. As noted in the response to the above comment, the cited sentence has been removed from the diagnostics guidance document.

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Comment number	Name and organisation	Section number	Comment	NICE response
20	DYSIS Medical Ltd.	4.13	(Page 18) The text should be edited, to clarify that "test failure rates" also include failures irrelevant to the technologies (e.g. biopsy results missing, etc.)	Thank you for your comment which the committee considered. Section 4.14 of the guidance document has been amended to clarify that the test failure rates mentioned include failures not related to the technology.
21	DYSIS Medical Ltd.	4.16	(Page 18): To adequately describe the study design, we suggest that *"(by the same colposcopists)"* is added after *"assessed with standard colposcopy"*, as this is an important aspect of the study design.	Thank you for your comment which the committee considered. Section 4.17 of the guidance document has been amended as suggested.
22	DYSIS Medical Ltd.	4.27	Page 21: Please change *"unknown"* to *"not reported in the abstract"*.	Thank you for your comment which the committee considered. Section 4.28 of the guidance document has been amended as suggested.
23	DYSIS Medical Ltd.	4.27	***"Of the colposcopists who filled in the questionnaire, 96% agreed or strongly agreed…"*** *(pages 21-22)* Please edit the entire paragraph so that it correctly reflects that the percentages reported were percentages of colposcopist responses not of colposcopists. So, it should be reading as • *"in 96% of the returned questionnaires the colposcopists agreed…"*	Thank you for your comment which the committee considered. As noted in the quoted text from the guidance document, this section already specifies that the figures refer to colposcopists who returned the

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Comment number	Name and organisation	Section number	Comment	NICE response
			• *"in 48% of the cases the colposcopist agreed that…"* • *"in 58% of the cases the colposcopists said they…"*	questionnaire. The committee considered that no changes to the diagnostics guidance were needed.
24	DYSIS Medical Ltd.	*4.45*	***"Indirect comparisons suggest that Zedscan I always costs more but is more effective than DYSIS in both 'see and treat' and 'watchful waiting' clinics. The results of the HPV primary screening base case were similar to the HPV-triage base case."*** *(Page 29)* Please edit this statement to clarify that this is based on limited evidence, e.g. to *"Indirect comparisons based on the limited available data suggest that Zedscan I always…"*	Thank you for your comment which the committee considered. The committee heard from the EAG that because of the lack of a direct comparison of diagnostic accuracy between the DYSIS and ZedScan devices, any results from the model comparing the technologies should be considered exploratory in nature. Section 4.46 of the diagnostics guidance document has been amended to further clarify the model outputs.
25	DYSIS Medical Ltd.	*4.4*	Page 13: insert *"at"* before *"a single centre".*	Thank you for your comment which the committee considered. Section 4.4 of the guidance document has been amended as suggested.

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Comment number	Name and organisation	Section number	Comment	NICE response
26	DYSIS Medical Ltd.	4.28	***"the EAG noted that this was based on a small subgroup analysis of the retrospective review of stored images".*** *(page 22)* This is the analysis that best relates with the subject matter- the detection of high-grade lesions. Notably, the results for assessing CIN2+ had statistical significance ($p<0.05$) for all colposcopist experience levels, so we kindly asked that this is also mentioned.	Thank you for your comment which the committee considered. The committee heard from the EAG that the current text is an accurate description of this study. The committee considered that no changes to the diagnostics guidance were needed.
27	DYSIS Medical Ltd.	*4.28*	***"Training Requirements"*** *(page 22)* The title "Training Requirements" is confusing as it has nothing to do with the study presented, which is a survey linking clinical assessments and colposcopist experience level.	Thank you for your comment which the committee considered. This section heading has been amended to 'Colposcopist experience'.
28	DYSIS Medical Ltd.	5.7	*"**noted a lack of detail on the methods used to ensure that controls in the retrospective arm were comparable to the cases in the prospective arm".*** *(page 36)* Comparing the patient baseline characteristics (Table 1 in the article) shows that the groups had virtually identical characteristics, so (given the large sample size and the consecutive recruitment) no further propensity matching or regression analysis was considered necessary, as there were no differing factors to bias results.	Thank you for your comment which the committee considered. The committee heard from the EAG that that the 2 study arms of this trial appear to be comparable on key baseline characteristics. Section 5.7 of the guidance document has been amended to reflect this.

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Comment number	Name and organisation	Section number	Comment	NICE response
29	DYSIS Medical Ltd.	5.10	***"The committee concluded that, in the absence of clinical-outcome data, or data on the natural history of low-volume CIN 2, there was currently uncertainty about the longer-term outcomes associated with the increased sensitivity of the adjunctive colposcopy technologies and wished to encourage further data collection to resolve this."*** *(page 37)* Please add statement that *"all available evidence on DYSIS suggests that the additional disease being detected is clinically important as opposed to low-volume and potentially regressive (i.e. on younger patients) CIN2 lesions."* To support this: • Zaal et al *BJOG* 2012; Table 3 shows a high sensitivity with the DYSISmap on patients with HPV16, the most oncogenic type of the virus • Louwers et al *Gynecol Oncol* 2015; Tables 2b & 3c show a high sensitivity with the DYSISmap for CIN3+, a better surrogate for cervical cancer than the histologically equivocal and potentially regressive (on younger women) CIN2 • Cholkeri-Singh et al, *J of the Lower Gen Tract Dis*, in press; Table 2 shows the increase in detection of CIN3+ is better than the increase for CIN2+, and is more pronounced in women >30 years old DeNardis et al, *Int J Women's Health* 2017; Tables 2 & 3, showing a high sensitivity with the DYSISmap for all age groups, all referral types, and also for CIN3+.	Thank you for your comment which the committee considered. The committee noted the additional information provided, but considered that additional data were needed to resolve uncertainties about the longer term outcomes. This is highlighted in research recommendation 6.4. It decided that no changes to the guidance document were needed.

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Comment number	Name and organisation	Section number	Comment	NICE response
30	Royal College of Pathologists		Diagnostic biopsy: Does the cost include the time taken for taking the biopsy and laboratory costs including use of p16?	Thank you for your comment which the committee considered. The committee heard from the EAG that the NHS reference costs they included in the economic model include histology/pathology costs. In addition, further additional sensitivity analysis were done in which additional costs for histology/pathology were assumed. These additional costs did not have a significant effect on conclusions.

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THEME: General comments

Comment number	Name and organisation	Section number	Comment	NICE response
31	DYSIS Medical Ltd.		Dear NICE Committee, Thank you for the updated Diagnostics Consultation Document provided for our review. In reviewing the updated Document, we have listed our comments below, some of which were already included in our previous communications, but were not fully addressed. We would also like to bring to your attention that, since the last meeting, the two articles from the IMPROVE-COLPO study have been published and are available on the journal websites: • http://journals.lww.com/jlgtd/Abstract/publishahead/Digital_Colposcopy_With_Dynamic_Spectral_Imaging.99514.aspx • https://doi.org/10.2147/IJWH.S144577 Also, the case report article by Kaufmann et al, previously submitted as a draft, has been accepted for publication by *Case Reports in Obstetrics and Gynecology* (uncorrected journal proofs are attached with this response as Academic In Confidence) With respect, DYSIS Medical Ltd.	Thank you for your comment which the committee considered.

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THEME: General comments

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32	Royal College of Pathologists		The diagnosis of CIN2 is difficult and varies between pathologists and laboratories. Judicious use of p16 with understanding of the limitations of the test, should be advised to ensure robustness of diagnosis of CIN2+. Gage JC, Schiffman M, Hunt WC, Joste N, Ghosh A, Wentzensen N, Wheeler CM; New Mexico HPV Pap Registry Steering Committee. Cervical histopathology variability among laboratories: a population-based statewide investigation. Am J Clin Pathol.2013;139(3):330-5 Singh C, Manivel JC, Truskinovsky AM, Savik K, Amirouche S, Holler J, Thyagarajan B, Gulbahce HE, Pambuccian SE. Variability of pathologists' utilization of p16 and ki-67 immunostaining in the diagnosis of cervical biopsies in routine pathology practice and its impact on the frequencies of cervical intraepithelial neoplasia diagnoses and cytohistologic correlations. Arch Pathol Lab Med. 2014;138(1):76-87 Clinton LK, Miyazaki K, Ayabe A, Davis J, Tauchi-Nishi P, Shimizu D. The LAST guidelines in clinical practice: implementing recommendations for p16 use. Am J Clin Pathol. 2015 Dec;144(6):844-9 Darragh TM, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012;136(10):1266-97	Thank you for your comment which the committee considered.