NICE National Institute for Health and Care Excellence

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities (update of DG4)

Diagnostics Assessment Report (DAR) - Comments

Please note: Where our responses suggest changes will be made, these will be provided in an erratum at a later date.

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
DYSIS Medical Ltd	1	28 106 199 171 176	1.6 4.6.4 8.1	The Report states that '*the use of DYSIS (…) could lead to an increase in the number of unnecessary diagnostic biopsies, excisions and "see and treat cases*"…… ' Also, Tables 57 & 61 (p.171/176) suggest that: • With DYSIS there is a significant increase in unnecessary treatments across LG and HG Referrals in clinics with a "see and treat" policy, presumably due to additional false positive indications. • "See and Treat" is practiced on women with a LG referral at "See and Treat" clinics, which is against National Guidelines (NHSCSP Publication 20 / 2016, p.57: See and Treat Policy) and contradicts the description in section 6.4.3.1 (p.147).	We will remove the text "*excisions and "see and treat cases*"" where this appears in the report in the erratum document. We still consider, however, that the evidence points to DYSISmap producing more "Test positives" than conventional colposcopy (see figure 11), so an increase in the number of diagnostic biopsies is plausible. We also note that, in clinics using "see and treat" such excisions may be performed on the basis of high grade cytology and colposcopy (without diagnostic biopsy). In such practice conditions using DYSISmap could therefore increase the rate of "see and treat" even if this is not recommended practice.

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				There is no evidence, in any type of clinic or any sub-population, to suggest that the DYSISmap drives a colposcopists decision to perform a 'See and Treat' procedure that would not otherwise have been performed (thus causing an overtreatment when the indication is a False Positive). Hence, the increase in unnecessary treatments (and resulting negative outcomes) depicted in the tables is unjustified. Such practice would be against the DYSIS indications for use, National Guidelines and colposcopic practice in England. Therefore, the above statement is incorrect and we request that it is removed from the final document. Furthermore, in "see and treat" clinics, women with a LG referral should always have a diagnostic biopsy first (similar to "watchful waiting" clinics), there should be no overtreatments among them and the Tables should be corrected to reflect this. There are many factors that influence the decision to 'See and Treat', such as: • Referral reason and Screening/ colposcopy history	In the economic model, "See and treat" is not assumed to be practiced on women with LG referral (see section 6.4.3.1). In the model, the decision to treat at first appointment does not depend on the device used for colposcopy. However, the lower specificity of DYSIS compared

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				• Demographics (Age, Parity, Smoking status) • Colposcopic impression and size of lesion • Patient compliance / possibility of future DNA • Local practice A biopsy is assumed to be 100% sensitive and specific, so these patients should be assumed to be never over-treated, but to receive an accurate diagnosis to ensure appropriate management and / or appropriate treatment. Biopsy itself does not have negative impact on future obstetric outcomes. Whilst we understand the comment that an increase in the number of unnecessary biopsies due to additional false positive indications is possible, this will depend heavily on the individual colposcopists current practice. KC65 2015-16 data reports biopsy rates in England ranging from: • 8% - University of Aintree • 83% - Royal Bournemouth Hospital	to colposcopy alone increases the number of false positive cases. In a "see and treat" clinic, these patients will receive unnecessary treatment. In tables 54 to 61 and 76 to 131, LG and HG referrals refer to the initial reason for referral. Unnecessary treatments may occur in subsequent colposcopy examinations if patients are referred as HG (test of cure, 6 months follow-up or routine screening). Tables 57 and 61 are therefore correct. In the model, the decision to treat at first appointment does depend on the referral reason and screening/ colposcopy history. Practice heterogeneity in terms of patients' demographic characteristics and preferences is not modelled.

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				• 47% - National average Current evidence from DYSIS users (e.g. QEH Gateshead, see Natsis et al BSCCP 2016 and Musgrove Park Hospital, see Founta et al IFCPC 2017) suggest there is no increase in biopsy rate.	In the model, diagnostic biopsy is not assumed to be associated with adverse obstetric outcomes. The increased risk of pre-term delivery is only applied to women who received treatment (LLETZ).

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DYSIS Medical Ltd	2	152	6.4.5.1. Device costs	The Report states that 'for DYSIS, annual maintenance costs included the DYSIS Viewer Registration and renewal, as well as a 5-year service and maintenance plan. ' DYSIS Viewer is an OPTIONAL, separate product to facilitate remote viewing of DYSIS dynamic colposcopic images at a PC, post-colposcopy. It is NOT required to perform DYSIS Colposcopy or DYSISmapping, so should be removed from any calculations. The DYSIS Preventative maintenance package is OPTIONAL. This is intended to provide "peace of mind" to owners that opt for it, at a fixed controlled cost to allow correct NHS budget forecasting. For parity, the optional maintenance costs for DYSIS should be removed from any calculations.	In the base case, the viewer licence is included as an additional yearly cost. In the absence of information on the average yearly maintenance cost, the base case includes the "optional maintenance package" in the purchase price of DYSIS. The cost of colposcopy alone includes a yearly maintenance cost (£1073 per year). We believe it would not be appropriate to consider a null maintenance cost for DYSIS only.
DYSIS Medical Ltd	3	153	6.4.5.1 Table 37	In relation to comment No 2 above (for maintenance and DYSIS Viewer), the costs in Table 37 for DYSIS are incorrect.	In table 37, the "purchase price" includes the price of DYSIS Touch and the maintenance package (£24,000 + £6500).

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				The purchase price of DYSIS Touch is £24,000 and *not* £30,500 as stated in the table. The Annual Maintenance cost for DYSIS stated at £530 is incorrect. DYSIS has a one year full Manufacturer's warranty and offers an OPTIONAL 5-year preventative service and maintenance package, offering additional protection to the user against manufacturing defects from year two onwards. This costs £6,500 for 5 additional years (i.e. for a total of 6 years). Disposables cost per patient for DYSIS is correct. The total cost per patient of £9.24 is incorrect, given the above.	In table 37, the "maintenance cost" is actually a yearly cost. In the case of DYSIS, £530 refers to the average annual cost of the viewer licence ((650+500*4)/5). In response to comments no.2 and 3, we provide an additional scenario analysis in a separate addendum where the cost of DYSIS includes only the purchase price of DYSIS Touch (£24,000) and a yearly maintenance cost equivalent to the maintenance cost of colposcopy alone (£1073 per year). In this scenario, the total cost per patient for DYSIS is £8.55 (instead of £9.24).
DYSIS Medical Ltd	4	39	2.3	The Report states that "*The manufacturer estimates that each cervical scan using the ZedScan takes 2–3 minutes*". This time is extra to the colposcopy / colposcopic assessment, and over a typical NHS colposcopy clinic of 10 patients, it costs an additional 30-minutes (roughly corresponding to 2 patients or	No additional clinician and clinic time were assumed when using Zedscan. It is also unclear whether 2-3 minutes additional scan time would lead to longer clinic appointment times or

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				20%). In contrast, DYSISmapping is performed in the background, in parallel with visual colposcopic assessment (aceto-whitening), without adding clinician time. Please confirm that this additional clinician and clinic time, when using ZedScan, is accounted for within the Model.	whether this could be accommodated within existing clinic schedules.
DYSIS Medical Ltd	5	27 83 167 172	1.1.4 4.3.4.6 6.6.1.1 6.6.1.2 and related Tables	The comparisons between DYSIS and Zedscan, and the corresponding conclusions are not scientifically sound (for reasons acknowledged and analysed in the Report) and should therefore be removed as they can be misleading, especially if taken out of context. Furthermore, these comparisons did not form part of the agreed scope (Final Scope Document) that stated (Table 3) that the Comparator should be Conventional Colposcopy.	We have made it clear throughout the report that comparisons between DYSIS and ZedScan are based on very limited evidence. We do not consider the evidence presented to be misleading, and have therefore not removed it from the report. That the scope specified the comparator as conventional colposcopy does not preclude making comparison between the new technologies. Indeed, we consider it necessary to make the comparison to fully inform the committee of the relative benefits and costs of the technologies.
DYSIS Medical Ltd	6	91	4.3.5.4	The use of the term “Test failure rates” is misleading as it includes cases that have been	

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				excluded from analysis in the corresponding manuscripts for reasons unrelated to the actual test (e.g. study protocol violations such as biopsies analysed together, biopsies not classified, wrong biopsy taken, missing histology). Please consider removing those cases, or changing the terminology.	Test failure was understood both as related and unrelated to the adjunctive colposcopy technology. This was clarified p90, last paragraph
DYSIS Medical Ltd	7	21 24 27 etc	Abstract - Results	The term 'Watchful Waiting' that is used frequently throughout the document does not accurately convey the scenario of taking a biopsy and awaiting the histological result prior to further management decisions. The term 'Watchful Waiting' could be misinterpreted as a true 'Conservative Management' approach. We suggest you consider changing this term to 'awaiting histology results of biopsy' or similar.	The term "Watchful waiting" is formally defined in section 6.4.3.1. It refers to a situation where the colposcopy result is always confirmed by histology before the decision to treat the patient is made. However, we acknowledge that the term could be misinterpreted and that an alternative term may be preferable.
DYSIS Medical Ltd	8	20	Abstract	The term 'Adjunctive DYSIS' that is used throughout the document, although correctly defined in the Glossary, is misleading because it may suggest that a colposcopy with DYSIS is additional to a "traditional" colposcopy with a binocular colposcope. Please consider changing to 'DYSIS Colposcopy' with the same definition.	The term "adjunctive DYSIS" was used to avoid cumbersome repetition. We consider the term to be clearly defined (e.g. in the glossary). We think that the alternative "DYSIS colposcopy" may be taken to mean the video colposcope only (without DYSISmap), and so be more confusing.

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DYSIS Medical Ltd	9	66	4.3.4.1	"The summary PPV, and the estimated PPV in most studies, is lower than the 65% level recommended by UK guidance. (15)" It is widely acknowledged that the PPV is a poor measure of the overall colposcopic performance as it depends on the population (disease prevalence) and the colposcopist. As quoted and presented by Prof. J. Tidy at the BSCCP advanced Colposcopy Course, Birmingham (Nov 17, 2016) "PPV outcomes can be 'gamed' by colposcopists by 'under calling' of suspected HG lesions". PPV is not used as a quality measure in other countries, so the result in these studies may be more objective. Please consider amending the text to better reflect the use of PPV.	The comment on PPV was added at the request of NICE. Therefore we have not amended it. It is intended to highlight potential differences between UK practice and that in the included studies (see section 4.6.1). We agree that PPV is a poor measure of diagnostic performance, which is why it is not considered in the primary models.
DYSIS Medical Ltd	10	54	4.3.1	"One study of test-of-cure patients reported a high prevalence of high-grade referral (84.7%), (51)" All patients in that study (51) were hrHPV+/Cytology-, so **not** High-Grade referrals.	The sentence and Table 4 will be amended.

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DYSIS Medical Ltd	11	42	4	"Clinical effectiveness" is used in a way that is inconsistent and could be misleading. In places, it includes diagnostic accuracy (section 3.2, p.41, section 4, p.42), elsewhere (Table 3, p.52, section 4.4, p.95) it refers to negative outcomes only (e.g. morbidity, adverse events, etc.). We believe that in the context of negative outcomes, the use of "Clinical effectiveness" is misrepresenting.	We accept that this could be misunderstood. As it is not a factual error no changes will be made.
DYSIS Medical Ltd	12	35	2.2.5	The report states "*Video colposcopy may also be used, particularly for DYSIS where the DYSISmap is overlaid onto a video colposcopic image, and it is unlikely that a separate binocular colposcopy will be performed."* No separate binocular colposcopy is performed – DYSIS *is* a digital colposcope. This inference could be misleading, please improve wording.	We will amend this to read: *…and no separate binocular colposcopy…*
DYSIS Medical Ltd	13	60	4.3.2.2	The Report states that *"Risk of study selection bias was considered high in both studies, notably due to the exclusion of patients with transformation zone type 3 in whom colposcopy may be harder to perform."* Further to this comment, it has to be noted that in Ref (94) the proportion of patients with High-	The fact that recruitment was not consecutive was already noted and reported in appendix 10.7, and supported the risk of bias judgment for this study. The prevalence of HG referrals in Tidy (2013) phase 2 (43.7%) was not considered sufficiently high compared with the national average to

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				grade referral is markedly higher than in other studies, and recruitment to that study was non-consecutive (page 2 of original paper), raising questions about patient selection methodology, to what extent this data is representative, and also suggesting data may not be comparable to other studies.	introduce significant bias or raise significant concerns about applicability of the diagnostic accuracy results of ZedScan+Colposcopy vs. colposcopy alone.
DYSIS Medical Ltd	14	89	Table 16	Table 16, footnote @: in Ref (80) the reported PPV that is quoted here should not be confused with the diagnostic PPV, as in that specific analysis (Ref 80) it refers to the PPV on the level of single biopsy, and not on the patient level (as is common).	A comment will be added to the footnote of this table. We note that this distinction was not clear in (80)
DYSIS Medical Ltd	15	95	4.4.1	Please add Ref (80), which also reports that there were no adverse events with DYSIS.	Number of studies included in the review of clinical outcomes was updated accordingly.
	16	88-89	Table 16	Table 16 - the sensitivity results from Ref (80) are presented in ways that are inconsistent (internally and to other studies), as they mix data from Table 1, referring to impression/prediction and Figure 2 that refers to detection by biopsy.	This distinction was not clear in the poster (80). We have made the best judgment of results we can, given limited information. We note this data was not used in any meta-analyses.
DYSIS Medical Ltd	17	281	Table 70	On the analysis of the Soutter (2009) study the Report states "*Principal investigator has an ownership interest in Forth Photonics"*, which is incorrect. The principal investigator (Mr P.	"Principal investigator" will be changed to "last author"

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				Soutter) ***never*** had any ownership interest in FORTH PHOTONICS (now DYSIS Medical).	
NHS Professional	18	199	8	**The Understanding of See and Treat and Unnecessary Treatments.** The conclusions on page 199 suggest a fundamental lack of understanding as to how DYSIS is used by clinicians. Few, if any clinicians, would perform a treatment based on the DYSIS map alone. The taking of additional biopsies may be a result, but my understanding of published evidence is that the biopsy rate is actually reduced. The 24-month data from my own unit showed no significant change in biopsy rate, which is indeed highly variable between colposcopy units, and individual colposcopists. The salient point is that guided biopsy leads to a targeted histological diagnosis. As a consequence only those women with proven high-grade disease will go on to be treated. As such an increase in unnecessary treatments cannot be a resultant conclusion.	We will delete “excisions and “see and treat” cases”, also see comment above.
NHS Professional	19	171	6.6.1.1	**Clinical Validity of Table 57.** I have concerns over the validity of the data in this table. Treatments rates across all grades of	The outcomes reported in tables 57 & 61 cannot not be compared with yearly see and treat rates for 3 reasons:

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				referral, and all technologies appear to be very high. Benchmarking against the 20 colposcopy units in my region; using colposcopy alone the see and treat rate in high grade referrals is approximately 60%, or 600/1000 compared to the 879/1000 quoted. With regard to low-grade referrals the figure is between 12-15%, or 120-150/1000 compared to the 276/1000 quoted.	(i)The number of LLETZ reported in tables 57 & 61 includes all treatments, received either before or after histology. Therefore, it cannot be interpreted as a see and treat rate. (ii)The see and treat rates reported in the comment (60% for HG, 12-15% for LG) reflect the heterogeneity in treatment decisions within and across units. As described in section 6.4.3.1, we model this heterogeneity with two different types of clinics. The implication is that, in ST clinics, all HG referral with a positive colposcopy result will be treated at first appointment. The large proportion of CIN2+ in HG referrals (about 80%) explains the high rate of treatments. Another implication is that LG referral will never be treated at first appointment. The 276/1000 quoted in table 57 refers to the average number of treatments (before or after histology), for 1000 cases with an initial LG referral over 60 years.

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					(iii) The simulation takes into account not only the outcome of the initial referral but also subsequent follow-ups and screenings for a period of 60 years. A comparison with "snapshot data" is therefore not appropriate.
				The quoted incidence and death rates of cancer appears to be very high in what is a screened and actively managed population.	The natural history data and transition probabilities were derived from a widely used epidemiological model by Kulasingam (2013) which was developed to inform the United States Preventive Services Task Force (USPSTF) on cervical cancer screening. The impact of screening on cancer incidence is taken into account in the model by linking screening and treatment outcomes to the natural history. As regards the parameter value, we provide additional sensitivity analyses where the annual probability of progression from CIN2/3 to Cancer is 1% (reported rate for women under 30) instead of 4%. We also consider the impact of age by using the age

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				With regard to premature delivery, no reference is given to gestational age and prematurity, the prime determinant of perinatal mortality and morbidity. Perhaps a better measure would be significant pre-maturity (less than 34 weeks) and extreme prematurity (less than 28 weeks).	distribution of women referred for colposcopy instead of an average age of 36. The results of these are reported within the separate addendum. The reference we use for QALYs and costs associated with premature delivery consider a threshold of less than 37 weeks (see sections 6.4.6.4). The excess risk of preterm birth, derived from Kyrgiou (2016), is therefore based on the same definition of prematurity (<37 weeks).
NHS Professional	20	Multiple	Multiple	**Definition of watchful waiting.** I would request a change in nomenclature for watchful waiting. I believe in your document this relates to when a biopsy has been taken and histological diagnosis is awaited. This is separate to conservative management that maybe mistakenly misunderstood as watchful waiting by clinicians. Examples of conservative management would be delay in treatment of high-grade disease due to pregnancy or patient choice, which in CIN 2 is becoming increasingly common.	Please see response to comment no.7.

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NHS Professional	21	199	8	**Response rate for patient satisfaction.** The conclusions on page 199 also suggest a possible increase in un-necessary patient anxiety. My unit was responsible for coordinating one of the largest patient satisfaction surveys in colposcopy that was presented by poster at the RCOG World Congress 2016. The patients were split into those that had never had a colposcopy (433/763) and those who had a prior traditional colposcopy and were then reviewed using DYSIS (330/763). The conclusions were DYSIS was well received, was not intimidating, improved the patients understanding of their condition. Given this I cannot see how the conclusion regarding anxiety has been made. If the conclusion relates to potential un-necessary biopsy/treatments this should be re-considered given my concerns in 1 above.	We meant anxiety due to having a false positive DYSIS test result (and therefore fearing they might have cancer), not anxiety from the DYSIS procedure itself. We will clarify in Section 8.
Zilico Ltd	22	20	Abstract : Results	Only 2 ZedScan references are included in the diagnostic review. While Reference 94 does give results obtained using the pre-commercial version of ZedScan, none-the-less the method of measurement and the analytical algorithm used by ZedScan are based directly on the pre-	Reference 94 (Tidy 2013) is included in the review of diagnostic accuracy. The paper did not report any data required for inclusion in the “clinical effectiveness” or implementation

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				commercial version and the logical pathway described in reference 94. We can see no reason why the results from reference 94 cannot be included in the clinical effectiveness and implementation reviews. Reference 94 describes the two methods used to determine the diagnostic accuracy figures for Colposcopy. The first method (CI method) returns a positive test result when the colposcopist considers that CIN2+ is present. A negative test result may be returned even though the colposcopist takes a biopsy to exclude the possibility that disease may be present. The second method (DP method) returns a positive test result if a biopsy is taken because it is thought that there is some disease present. The DP method returns much higher sensitivity figures than the CI method but lower specificity figures. When making comparisons between DYSIS and ZedScan the same method of calculating the diagnostic accuracy figures must be used. DYSIS uses the CI method but the figures given in Table 1 of reference 103 use the DP method. The comparable figures for ZedScan performance are:	sections (such as adverse event or patient satisfaction data). Our understanding is that we have used the most appropriate diagnostic accuracy data for the comparison. For ZedScan we used the data provided by Zilico from the Tidy EJOG study (2017) (Ref 103). Table 2 in that paper describes the analysis as “Colposcopic Impression TP FP and/or ZedScan”, and the methods section states that “the authors correlated colposcopic impression at the site of biopsy whether colposcopically directed or ZedScan I directed, to the biopsy outcome”. Therefore we assumed that these most recent data represented the best (and

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				When using the CI method (see reference 94 Table 2) adjunctive ZedScan use was found to have the same sensitivity for detecting CIN2+ lesions (73.6%) as standard Colposcopy alone (73.6% 95% CI 63.0 to 82.5%) but higher specificity (90.8%) than colposcopy alone (83.5% 95% CI 75.2 to 89.9%). **When using the DP method (see reference 94 Table 3 and reference 103 Table 1)) adjunctive ZedScan use was found to have an increased sensitivity for detecting CIN2+ lesions (97.9% 95% CI 96.6 to 99.2%) than standard Colposcopy alone (88.5% 95% CI 79.9 to 94.4%) and higher specificity (58.4% 95% CI 55.1 to 62.1%) than standard Colposcopy (38.5% 95% CI 29.4 to 48.3%).** The use of the correct figures for sensitivity and specificity for ZedScan in comparison with DYSIS affects several figures and text elsewhere in the NICE document. This will affect the both performance and probably cost figures as these depend on the numbers of biopsies related to	indeed only) current diagnostic accuracy estimates (in CI terms) for ZedScan I. These are the results presented for ZedScan in Table 9 and Figure 10. We believe we have used the most appropriate diagnostic accuracy data throughout, as provided to us directly by Zilico. As noted above the results in Table 1 or 2 of reference 103 appear to be for the CI method. They appear to be compared to DP colposcopy results from reference 94 in Table 3 of reference 103, but that does not mean the results for ZedScan were for the DP approach.

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				false positives. Use of the correct comparative figures will certainly result in changes to Tables 17 (Page 89) and 25 (Page 142) and probably Tables 19 (Page 93) and 57 (Page 171).	
Zilico Ltd	23	25	1.4.1	In para 4 it is stated that both ZedScan studies were performed by the same researchers at Sheffield. This is incorrect. The study using the pre-commercial prototype (ref 94) was conducted at three centres – Sheffield, Manchester and Dublin – by a single,	We note that the lead authors on both papers are the same, so therefore the same researchers were involved, even if other researchers were different.

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				different colposcopist at each centre and in Phase 2 approximately equal numbers of patients were recruited at each centre. The second paper (ref 103) was written by some of the same authors as the previous paper but this presents the results of a service evaluation within a routine NHS colposcopy clinic where 93% of the patients were examined by 3 nurse colposcopists who were not involved in the earlier work or any previous research. The rationale was that it was important to determine whether the potential benefits identified in the previous paper could be replicated by using ZedScan in a normal clinical setting. It is well-known that the results obtained in clinical trials can often be difficult to replicate in normal use; e.g. Zwarenstein M., Oxman A. Why are so few randomized trials useful, and what can we do about it? *J Clin Epidemiol.* 2006;59:1125–1126 and Patsopoulos NA. A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci.* 2011; 13:217-224	
Zilico Ltd	24	26	1.4.1	The failure rate of colposcopy due to patients with a Type 3 TZ is entirely dependent upon the population attending the clinic and is common for both conventional colposcopy and any current	We will amend this sentence.

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				adjunctive technology. For this reason we have quoted a failure rate that reflects the additional failures due to the use of ZedScan; the total failure rate will then depend upon the local prevalence of women with a Type 3 TZ. We believe that the DySIS publications probably provide sufficient information that the equivalent failure rate can be calculated.	
Zilico Ltd	25	26 99	1.4.3 4.5.2	Zilico was approached to provide contact details for colposcopists with experience of ZedScan. We wonder whether these clinicians were contacted and, if they were, why the report does not include any reference to their feedback.	The EAG did not request this, nor did we receive any such feedback. We are therefore unable to comment.
Zilico Ltd	26	27	1.4.4.	The statement is made here that 'See and Treat dominated colposcopy alone' when using ZedScan. This statement is correct. However, the reason why ZedScan is able to provide specificity greater than 90% when 'See and Treat' is considered is not explained. It should be made clear that, because ZedScan uses a method of template matching to expected impedance spectra, and electrical impedance spectroscopy enables different thresholds to either increase or decrease the probability that high grade CIN is present. Zilico has applied a high threshold (this threshold cannot be changed	The diagnostic accuracy of ZedScan is based on sensitivity and specificity reported in Tidy (forthcoming) (see response to comment no. 22). Although we acknowledge that ZedScan uses different threshold that may alter the sensitivity and specificity of the diagnostic, the only available data we were able to use to inform the model were average sensitivity and specificity reported in Tidy (forthcoming).

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				by clinicians) to ZedScan for 'See & Treat' patients, such that the specificity is increased to more than 90% so that See and Treat can be carried out with much more confidence than when using colposcopy alone and ensure compliance with the requirement of NHSCSP 20 that S&T has a PPV of >90%. Reference 103 reports that 273 women underwent treatment at first visit based on colposcopic impression of HG-CIN and a positive ZedScan I result and 260 (95.2%) had confirmed HG-CIN with 83.5% having CIN3+. **These data could be included in the Scientific Summary section (Page 23).**	As a consequence, in the model, the diagnostic accuracy of ZedScan is the same in See and Treat and in Watchful waiting clinics
Zilico Ltd	27	31	2.1	The last para of this section acknowledges that the prevalence of HPV 16 may affect the performance of colposcopy. Does the model take this into account and also consider the impact of vaccination with the associated reduction in the prevalence of HPV16 and 18? This could have a significant impact on the cost benefits of adjunctive technologies whose performance is dependent upon the prevalence of HPV16.	As HPV immunisation is new, very few immunised people will have entered the cervical screening programme or will have developed CIN or cervical cancer. For this reason the impact of HPV vaccination has not be considered in this assessment. (see section 7.4)
Zilico Ltd	28	38	2.3	The DYSISmap is described as an adjunct to colposcopy. Is it possible to use DYSISmap with binocular colposcopes or even with digital	We think the report is clear that DYSISmap is used with DYSIS colposcope.

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				colposcopes other than the DYSIS high resolution digital video colposcope? If not then the DYSISmap should be described as an adjunct to the DYSIS colposcope.	
Zilico Ltd	29	40	3	Para 3 states implies that ZedScan (or APX100) was reviewed in the DG4 assessment which is not correct. APX100 was dropped from the review process at an early stage due to a delay in obtaining the CE Mark and the full title of DG4 makes it clear that only the DYSIS and Niris technologies were reviewed.	This was a typo, and will be corrected.
Zilico Ltd	30	41	3.1	ZedScan can be used with any colposcope either a binocular optical instrument or digital video device. Majority of clinics in the UK will use a binocular colposcope as 3D visualisation is an important facility for clinicians to make a better diagnostic impression. Could the authors highlight if any studies have been published on the effectiveness of diagnosis and treatment using digital colposcopes? Zilico is aware that outside the UK some hospitals do use digital colposcopes primarily because they are cheaper.	The EAG found no published review evidence on the effectiveness of digital colposcopy. Clinical opinion was that there should be no difference from binocular colposcopy.
Zilico Ltd	31	52	Table 3	We are unclear as to how publications have been used in the assessment. This table includes the 11 studies referred to on page 20 as	Column heading in Table 3 should read “Publications included”. This will be amended. The number of references is

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				being included in the diagnostic review but there are many more references in the table in the columns headed 'Studies included in the review'.	larger as most studies had multiple publications (or conference abstracts).
Zilico Ltd	32	52	Table 3	The publication from Macdonald (ref 104) is referred to as 'submitted EJGO' whereas elsewhere in the report it is correctly referenced as Macdonald (2017)	This will be corrected.
Zilico Ltd	33	60	4.3.2.2	The studies reported in refs 94 and 103 did not take biopsies from patients with a normal cervix because the comparison was with normal colposcopic practice in the UK and it is considered unethical to take biopsies from apparently normal tissue unless there is a suspicion that disease might be present.	This does not affect the conclusion with regard to potential for bias.
Zilico Ltd	34	81	4.3.4.4	The primary HPV screening pilot does not include low-risk HPV types and based on the pilot these would not be included when primary HPV screening is implemented nationally from April 2019	No response required.

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Zilico Ltd	35	84	4.3.4.6	There is reference to a logistical regression model but there does not appear to be any description of how this was performed and we would like to understand what UK data was included in this. We note that the performance figures from Table 8 show a rather poor sensitivity for colposcopy which could lead to clinical practice where biopsies are taken even though the colposcopist has not identified the presence of disease. It is important that the reference performance of colposcopy is based on UK data because the UK (and the Republic of Ireland) has an effective QA system for colposcopists and accredited training programme. This is in contrast to most other countries e.g. The Netherlands. The EpiCIN trial data for the performance of colposcopy has been excluded as a comparator of the efficacy of colposcopy. When designing the EpiCIN trial the clinical leads at each centre (Professors, Tidy, Kitchener and Prendiville) considered the potential role of disease ascertainment bias however the conclusion was that the only ethical option was to compare the use of ZedScan against standard UK colposcopic practice. The EpiCIN trial was	The model is as described in Section 4.1.5.1 and reference 41. Only diagnostic data from the included diagnostic accuracy studies (Tables 3 and 4) was used in the model. UK colposcopy data were limited. The potential differences are noted in Table 14

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				designed so that each patient could act as their own control and so we were not studying the performance of colposcopy alone as one of the arms of the study. As a result we were of the opinion it was unethical to take random biopsies from normal 'colposcopic' tissue as this would lead to unnecessary morbidity (as demonstrated by the TOMBOLA trial). Colposcopy practice in England and Ireland has been shown to be highly effective. All colposcopists undergo a strict training programme with an exit exam. All colposcopy clinics take part in a national quality assurance programme and are assessed against standards of performance and care described in published evidence based national guidance documents. Colposcopy has been shown to be effective in the UK screening programmes as it has contributed to the significant reduction in incidence and mortality of cervical cancer. Furthermore the national audits of cervical cancer published by the English cervical screening programme have shown that failures in the colposcopic management of women make a minor contribution to the development of	

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				cervical cancer in women who have undergone a colposcopic examination. Given the international high regard for colposcopy practice in England and Ireland it seemed the most appropriate control for the EpiCIN trial was 'standard' colposcopy practice. There is however no formal training programme for colposcopy in the Netherlands, no quality assurance programme and no national standards of care. Given these differences is difficult to understand the relevance of the data from the Netherlands to UK practice. In some European countries and US centre there is a policy to take random biopsies to make up for the poor performance of colposcopy in their country. For the above reasons relating to the quality of UK colposcopy random biopsies from 'normal' tissue is not recommended. The authors of the report highlight the Louwers paper as having validity to the UK because the positive predictive value (PPV) of colposcopic impression exceeded 65%, the UK standard. The authors will also be aware the PPV is entirely dependent on the prevalence of the disease in the population being assessed and may have very	

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				little to do with the diagnostic accuracy of the test. There are multiple peer reviewed data, (Wentzensen N, Walker JL, Gold MA, Smith KM, Zuna RE, Mathews C, Dunn ST, Zhang R, Moxley K, Bishop E, Tenney M, Nugent E, Graubard BI, Wacholder S, Schiffman M. J Clin Oncol. 2015 Jan 1;33(1):83-9. doi: 10.1200/JCO.2014.55.9948. Epub 2014 Nov 24) showing that PPV for colposcopic impression falls with a decline in the grade of the referral cytology. Direct comparison of PPV to justify the validity the colposcopy practice from the Louwers paper to UK practice is scientifically and more importantly clinically unsound. Colposcopy is an imperfect diagnostic test as the true disease status for any woman cannot be ascertained. To do so would require all women to undergo a LLETZ procedure to ascertain their true disease status. This is unethical as acknowledged by the authors. Directed biopsies have limitations in confirming disease status and have morbidity (Underwood M, Arbyn M, Parry-Smith W, De Bellis-Ayres S, Todd R, Redman CWE, Moss EL. Accuracy of colposcopy-directed punch biopsies: a systematic review and meta-analysis. BJOG 2012;119:1293–1301). In	

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				developing the EpiCIN trial we decided along with the research ethics committee it was acceptable to undertake biopsies from abnormal areas, colposcopic or EIS, but to take random biopsies from normal tissue was not as it was not part of normal practice in standard UK colposcopy practice, which was the comparator for ZedScan. The trial design was also important as the trial had to demonstrate any potential improvements when compared to standard UK colposcopy practice as this would be the clinical effect of using any adjunctive test in routine practice. We acknowledge the EpiCIN trial data can therefore be at times difficult to interpret.The role of NICE is to provide guidance to the NHS in England and Wales. The data for current colposcopic performance in UK practice in very limited. The only recent data is in fact the EpiCIN trial. Given the significant variations in colposcopy training, practice, lack of national guidance and quality assurance in around the world, except the UK and Ireland, it will be important for NICE to take this into consideration when making recommendations the are applicable to current colposcopy practice in	

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				England and Wales.	
Zilico Ltd	36	87	4.3.5.2	The important point presented in reference 104 is that using ZedScan leads to a significant increase in the detection of CIN2+ disease in HPV-positive women and this is mainly due to a significant increase in the detection of disease in women with high-risk HPV types other than type 16. A recent report - Munro A, Gillespie C, Cotton S, Busby-Earle C, Kavanagh K, Cuschieri K, Cubie H, Robertson C, Smart L, Pollock K, Moore C, Palmer T, Cruickshank ME. The impact of human papillomavirus (HPV) type on colposcopy performance in women offered HPV immunisation in a catch-up vaccine programme: a two-centre observational study. BJOG 2017; DOI: 10.1111/1471-0528.14563 - shows a reduction in colposcopic performance in women who have been vaccinated against HPV16 and	No response needed.

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				18. This will be true in England from 2020 when women entering the screening programme will have been vaccinated against HPV. The disease they will have will be associated with the other high risk HPV subtypes and less amenable to detection by colposcopy increasing the needs for adjunctive technologies that are independent of HPV subtype.	
Zilico Ltd	37	95	4.4.2	The meta-analyses by Kyrgiou use data from earlier publications on the reproductive outcomes of treatment for CIN. The authors acknowledge the conclusions may not be applicable to the UK. More relevant data for the UK have been published from the English cervical programme. Why has this data not been incorporated into the model as it shows a less significant adverse risk of premature labour in women treated in the UK? Risk of preterm birth following surgical treatment for cervical disease: executive summary of a recent symposium. Sasieni P, Castanon A, Landy R, Kyrgiou M, Kitchener H, Quigley M, Poon L, Shennan A, Hollingworth A, Soutter WP, Freeman-Wang T, Peebles D, Prendiville W,	We believe that the meta-analysis published by Kyrgiou in 2016, which includes 26 studies focusing on the specific impact of LLETZ on adverse obstetric outcomes (N=1,445,341), provides stronger evidence than a single UK-based study (Castanon, 2014) (N=1598). Note that the relative risk of preterm birth for women who received treatment reported by Kirgiou (2016) (1.57), is in the confidence interval reported by Castanon (2014) (1.38, 1.10 to 1.72). Finally, scenario 2 (section 6.6.3.2) provides the base case results assuming that treatment would not have

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				Patnick J. BJOG. 2016;123(9):1426-9. doi: 10.1111/1471-0528.13839. Epub 2015 Dec 23. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, Walker P, Patnick J, Sasieni P; PaCT Study Group.BMJ. 2014 Nov 5;349:g6223. doi: 10.1136/bmj.g6223. Erratum in: BMJ. 2014;349:g7406. Risk of preterm birth after treatment for cervical intraepithelial neoplasia among women attending colposcopy in England: retrospective-prospective cohort study. Castanon A, Brocklehurst P, Evans H, Peebles D, Singh N, Walker P, Patnick J, Sasieni P; PaCT Study Group. BMJ. 2012 Aug 16;345:e5174. doi: 10.1136/bmj.e5174	any significant effect on preterm births (Castanon, 2012).
Zilico Ltd	38	101	4.5.3.2	In the UK virtually all treatment procedures e.g. LLETZ are performed under direct vision through a binocular colposcope. The use of a digital colposcope such as the DySIS instrument produces an image of the colposcopy on a flat TV screen and so treatments will not be under	The EAG found no published evidence on this. A comparison between digital and binocular colposcopes was out of the scope of the review. Clinical opinion was that there was no difference between video and binocular

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				direct vision. Have the clinicians made any comments, positive or negative, about treating patients in these circumstances? Do the clinicians feel happy treating patients indirectly via the TV screen? Do they remove the digital colposcope and use a binocular colposcope for treatment or do they always as the women to return for treatment and use a binocular colposcope? Are there any studies on the comparative effectiveness of treatment carried out using a digital colposcope? If UK clinicians are unhappy to perform treatments using a digital colposcope, each colposcopy clinic would still need to have an additional binocular colposcope that would need to be costed into the model. The flexibility and utility of DySiS may be limited by these issues.	colposcopy in terms of diagnostic accuracy.
Zilico Ltd	39	127	6.2	In paragraph 3 there is a statement “and (ii) the probability of a positive colposcopy result (CIN2+) is identical for Clear, HPV and CIN1 patients and for patients with CIN2/3 and invasive cancer.” As a colposcopist I do not understand this categorisation and so cannot comment on its validity.	In the model, a patient is characterised by a “true health state”: clear, HPV only, CIN1, CIN2/3 or cancer. The five categories are derived from the natural history model (see section 6.3.2.1) The colposcopy result is modelled as the probability of having a positive colposcopy, i.e. being diagnosed as

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					CIN2+, given the patient's "true health state". Because sensitivity and specificity are usually reported with a CIN2+ cut-off, we have to assume that the probability of being truly diagnosed by the colposcopist as CIN2+ (sensitivity) is the same for patients with CIN2/3 lesions and cancer. Similarly, the probability of being falsely diagnosed as CIN2+ (1-specificity) is assumed to be the same for patients who are clear, HPV only or CIN1.
Zilico Ltd	40	132/3	6.3.2.2	In the model the management of a woman is described as a patient characteristic. They are referred to either a see and treat clinic or a watchful waiting clinic. This presumes that the care of a woman is simply dichotomous and entirely dependent on the clinic policy. What evidence do you have to support this statement? What evidence is there in the UK as to the distribution of see and treat clinics versus 'watchful waiting' clinics? The NHSCSP and the national statistical return do not collect this data. Furthermore 'watchful waiting' will also be	The distinction between See and treat and Watchful waiting clinics is not a statement, it is a modelling assumption meant to deal with heterogeneity in treatment decisions. This assumption has been discussed and validated with clinical experts. In the absence of clear determinants for the decision to treat at first appointment and apparent variability across and

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				offered to women who attend see and treatment clinics even when referred with high grade cytology.	within clinics, we believe that presenting results for two clearly identified types of practice is more appropriate than an attempt of modelling the “average” colposcopy unit.
Zilico Ltd	41	136	6.3.2.3	The data for poor obstetric outcome quote for Kyrgiou is generally no longer accepted to be relevant to the UK given the publication by Castanon et al. which confirms women undergoing a LLETZ of 10mm or less, in the UK, do not have an increased risk of premature labour. The majority of women with a type 1 transformation zone will be treated to a depth of 8mm.	Please see response to comment no.37.
Zilico Ltd	42	147	6.4.3.1	It is stated that the most common outcome for women referred with high grade cytology is treatment at first visit. In the light of our previous comment (11 above) regarding the potential issue in carrying out treatment using a digital image rather than having direct vision, is there any data on the treatment outcomes when using DySIS? What is the risk of over or under treatment because the depth of excised tissue may be more difficult to control? Has cure rate been	We found no evidence on this.

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				determined? This also raises issues about the need for additional training and associated validation of treatment procedures when using a digital colposcope.	
Zilico Ltd	43	153	6.4.5.1	A colposcopy clinic in the UK must have a colposcope to undertake colposcopy. ZedScan is an adjunct to any current colposcope used in the UK, binocular or video colposcope (digital). The use of ZedScan does not require the purchase of a colposcope unless a new clinic is being established. The DySiS color map can only be used as part of DySiS videocolposcope. The DySiS color map system cannot be used with a binocular colposcope or any other type of videocolposcope. If a colposcopy clinic was to use the DySiS it must purchase the entire system, i.e. the DySiS videocolposcope and the colour map system. In addition the clinic must purchase the specific DySiS speculum, the DySiS system will not work without this specific speculum. If a clinic was to purchase a DySiS system it would need to 'write off' the value of its existing colposcope as part of the business plan. I cannot see any sensitivity analyses as to the cost per patient in section 6.4.2 (should this be section 6.5.2.2?)	We followed a similar approach to that used within the previous assessment of DYSIS (NICE DG4). That is, our analyses consider the cost-effectiveness of purchasing a DYSIS device rather than purchasing a new colposcope. A separate analysis might consider the cost-effectiveness of replacing a colposcope that has already been purchased. In this case, the per-patient costs of colposcope would exclude the annuitised cost of the colposcope (£1.60). However, it is not envisaged that this difference would materially affect our conclusions, particularly if the replaced colposcope has value and can be sold to contribute to the purchase of the new device.

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Zilico Ltd	44	153	Table 37	The table has two superscripts, a and b, but there is no explanation as to their significance. This table quotes a cost per patient. This is of course entirely dependent on the number of patients examined. There is a considerable heterogeneity in the number of women referred	Subscripts a and b are defined under Table 37. Subscript a indicates that that the purchase price of the equipment is annuitised over its life time assuming a 3.5% interest rate. Subscript b indicates that the total cost per patient is based on the assumption

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					that one device is used for 1229 patients per year. Please see section 6.4.5.1 for justification and sensitivity analyses SA5.1 & SA 5.2 for the impact of the number of patients examined on the cost of devices.
Zilico Ltd	45	171	Table 57	The authors have produce data using DySIS in a see and treat clinic. DySIS works by producing a colour overlap map that high lights area of potential abnormality and the colposcopist can take biopsies from these areas. The increased sensitivity using DySIS is related to taking biopsies from these areas. There are no UK publications describing the role of the DySIS colour map to predict the presence of CIN2+ at the time of see and treat. The authors appear to have extrapolated the data based on watchful waiting approach and suggest possible outcomes for see and treat. See and treat with DySIS is rarely performed given the lack of prospective data and the problems with the clinical utility of the system previously described. ZedScan has been used to predict the presence of CIN2+ at the time of see and treat and published data demonstrate its performance	An important objective of the model is to try to generalise from the diagnostic accuracy studies in order to determine the potential clinical and cost-effectiveness of the adjunctive technologies in different clinical contexts. Although we did not specifically derive data from See and Treat clinics for the purposes of informing our estimates of DYSIS, the underlying assumptions in our approach were explicitly stated.

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				exceed <90% as required by NHSCSP No20. No such data for DySIS has been published and so its validity in see and treat is currently unproven in the UK and this table overstates any potential use and so is misleading to the reader. These observations are also relevant to table 54. Section E of the KC65 return for colposcopy clinics in England report the percentage of women undergoing treatment at first visit (See and Treat). It records this data as 'non diagnostic' biopsies performed hence they are treatment biopsies i.e LLETZ at first visit. The latest national statistics 2015-16 (http://www.content.digital.nhs.uk/catalogue/PUB22414) show that see and treat performed by colposcopy only shows that only 87.9% of samples contained any CIN (this includes CIN1, CIN2, CIN3) so the rate of CIN2+ for see and treat is likely to be less than 87.9%. It is therefore difficult to accept the data in table 57 for the performance of colposcopy at the time of see and treat results in 879 LLETZ procedures and only 30 cases of unnecessary treatment. This does not fit with clinical outcomes are reported by NHSCSP.	The outcomes presented in table 57 & 61 include treatment at initial visit as well as treatments occurring during follow-ups or subsequent routine screenings for a period of 60 years. Therefore a direct comparison with NHSCSP annual statistics is not appropriate. Please see also response to comment no.19.

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				The relationship between the data in Tables 57 & 61 and the model is also unclear. We assume that the numbers in any row will not add up to 1000 because these are the outcomes over a pathway including follow-up and treatment appointments. Nevertheless it is difficult to understand how some of these numbers arise. For example in Table 57 for S&T clinics following the ZedScan strategy there are 916 women who undergo LLETZ (presumably at first visit or at a follow-up treatment appointment) but also 220 unnecessary biopsies; given that there are only 84 women who do not undergo LLETZ how is the figure of 220 arrived at? This is particularly difficult to understand as the model used appears to be dichotomous with women assigned to either See and Treat or Watchful Waiting clinics. If all 1000 women with high grade cytology are referred for See and Treat the number of LLETZ and biopsies taken should be close to 1000.	The relatively low number of unnecessary treatments for colposcopy is explained by its relatively higher specificity compared to DYSIS or ZedScan. Unnecessary biopsies can also arise for women who undergo LLETZ; for instance during test of cure of for subsequent screening. Moreover, the number of unnecessary biopsies cannot be interpreted as the proportion of women who received an unnecessary biopsy but only as the number of unnecessary biopsies performed for 1000 patients over 60 years. Indeed, one patient is likely to undergo several biopsies (the maximum in the model was 8 diagnostic biopsies for one patient over 60 years)

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					The number of diagnostic biopsies is not reported in Table 57. However, for the same reasons than above, the figures would not add up to 1000. On the contrary, for HG referral in ST clinics, the sum of LLETZ and diagnostic biopsies will necessarily be higher than 1000. Indeed, at first referral, all HG will undergo either treatment (if colposcopy is positive) or biopsy (if colposcopy is negative). Subsequent treatments and biopsies will add to these initial 1000 acts. For your information, the number of biopsies for colposcopy alone, DYSIS and ZedScan in ST clinics for HG referrals are 733; 533; 394.

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Zilico Ltd	46	172	6.6.1.2	The ARTISTIC trial demonstrated the increased sensitivity of primary HPV testing in detecting CIN2+. This trial is not similar to the current proposed hr-HPV primary screening algorithms where women who are persistent hrHPV-positive, cytology-negative are referred to colposcopy to confirm or exclude CIN2+ missed by cytology. This group of women has resulted in a 66% increase in referrals to colposcopy (HPV primary screening pilot data). In addition the prevalence of CIN2+ is low (5-13%) and so similar to women referred with low grade (mild) dyskaryosis. The performance of colposcopy to predict and identify disease (colposcopic impression) is dependent on the prevalence of CIN2+ in the referred population. For the hrHPV primary screening to be cost effective women who do not have disease need to be discharged from the colposcopy clinic back to routine community screening at first visit. The poor sensitivity of colposcopy prevents this from happening and so the use the adjunctive technologies with increased sensitivity and hence negative predictive value are going to be of considerable importance to the new screening programme.	No response required.

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British Society of Colposcopy and Cervical Pathology	47			On behalf of the BSCCP, I think it is very difficult to make valid judgements on the diagnostic performance of either DYSIS or Zedscan as the included studies all seem to have methodological flaws and they are different in their inclusion, exclusion criteria and parameters of outcome performance. It is difficult for an independent reviewer to determine the quality of many of the studies included in the review as they are unpublished and their characteristics are concealed in the tables for confidentiality reasons. Many of the DYSIS papers are from Gateshead but I cant see a baseline colposcopy sensitivity in this setting. The review has decided to take a baseline sensitivity of colposcopy at around 59% from the dutch Lowers paper but both a Zedscan paper has demonstrated a sensitivity of around 75% as has the Spanish Coronado Dysis paper. Both these studies have not verified colposcopy negative women but this reflects colposcopy practice in the current NHS setting. I therefore	No response required The summary estimates of sensitivity and specificity were based on the meta-analysis, not the Louwers study alone. We acknowledge in the report that this may not accurately reflect test performance in the UK, but verification bias issues limit our scope to investigate this.

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				feel that setting colposcopy sentisitivity so low will over inflate the benefits of DYSIS in comparison to Zedscan, furthermore it will inflate the benefits of new technologies in totality The majority of the studies are driven by their respective industry sponspor and therefore might be biased in their outcomes. It is interesting to note that the Spanish Corando and Danish Roensbo DYSIS studies which were independent of the company did not show such polarized results and in fact the latter study although methodologically flawed had negative results.	While this is correct we note that the Coronado study had more FAVOURABLE results than average for adjunctive DYSIS (e.g. compare Diagnostic Odds Ratios for Coronado study in Figure 5)

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British Society of Colposcopy and Cervical Pathology	48			The evidence base is too weak to make any definitive conclusions. The design of the included studies and the lack of independent verification potentially makes any recommendation flawed.	We think our conclusions are clear on this point.

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British Society of Colposcopy and Cervical Pathology	49			I think the authors of the review should set out a template for an optimal study in a Quality Assurred NHS setting bearing in mind that a gold standard diagnostic test study will not be feasible in such a setting. This would direct future studies so that they could bench mark performance whether colposcopy or adjuncts.	We have made some comments in the recommendations for research, but anything more detailed is beyond the remit of the EAG.

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British Society of Colposcopy and Cervical Pathology	50			There is NO evidence that a slightly higher sensitivity impacts on prognosis or outcomes. Patients with low volume CIN2+ that might be missed by colposcopy alone might have disease that might be destined to regress spontaneously. Only Randomised controlled of adjunct versus no adjunct trials with time for rescreening at 3 years might determine any true benefit from such technologies. Therefore the clinical impact on CIN2+ and invasive disease can not be determined A high Negative predictive value / specicificity results in women being discharged from colposcopy clinic to three yearly screening. This is an important parameter in a health economy and for patient re-assurance , I feel that that this aspect of performance is underplayed in the review.	The conclusions of the diagnostic accuracy meta-analysis and the economic model do consider trade-off between sensitivity and specificity.
British Society of Colposcopy and Cervical Pathology	51			I think the final conclusion for both products should highlight that there is no clear evidence base for either of them and that future evidence is required.	We would not consider the evidence base for DYSIS to be particularly limited (although of uncertain relevance for the UK). The limitations for ZedScan are acknowledged in the report.

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British Association for Cytopathology	52			Thank you for sending the updated draft on the above for comment. The review appears comprehensive and incorporates the many changes within the NHSCSP over recent years and the planned changes for the near future also. The BAC have no significant comments to add on this revised document. I apologise for the late reply from your requested timescale.	No response required (NICE response)