National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

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

This overview summarises the key issues for the diagnostics advisory committee's consideration. This document is intended to be read together with the final scope and the diagnostics assessment report. A glossary of terms can be found in appendix B. Academic in confidence data is [redacted]

1 Background

1.1 Introduction

DYSIS with DYSISmap (DYSIS medical) and ZedScan I (Zilico) adjunctive colposcopy technologies are intended to be used together with colposcopy to help identify cellular changes (known as cervical intraepithelial neoplasia [CIN]) during a colposcopy examination. Conventional colposcopy is a subjective examination which can be associated with both inter- and intra-observer variability, particularly with lower-grade abnormalities. DYSIS and ZedScan I aim to provide an objective evaluation of cellular changes using optical or electrical impedance spectroscopy to assess the characteristics of cervical cells. The DYSIS colposcopy system includes a video colposcope and an adjunctive DYSISmap, whereas the ZedScan I is used with a conventional binocular colposcope.

This guidance will update the existing guidance on adjunctive colposcopy technologies, which included the following recommendation: "DYSIS is a

clinically and cost-effective option, compared with standard colposcopy, for examining the uterine cervix in women referred for colposcopy, and should be considered in procurement plans for colposcopy equipment". Since this guidance was issued there have been changes to the CE-marked products as well as changes to the care pathway. The update has been done according to the standard update process.

Draft recommendations on the use of these technologies will be made by the diagnostics advisory committee on 27 July 2017.

1.2 Scope of the assessment

Table 1 Scope of the assessment

Decision question	What is the clinical and cost effectiveness of the adjunctive colposcopy technologies for assessing suspected cervical abnormalities?
Populations	People referred for colposcopy as part of the NHS cervical screening programme under either: • the human papilloma virus (HPV) triage screening algorithm (including test of cure), or • the HPV primary screening algorithm recommended for use in the sentinel sites (including test of cure). When data permits, the following subgroups may be considered: • People with an hr-HPV infection caused by genotype 16 • People with an hr-HPV infection caused by a non-16 genotype.
Interventions	• DYSIS with DYSISmap - this includes version 3, touch and ultra models. • ZedScan I. Both interventions are intended to be used together with conventional colposcopy examination.
Comparator	• Conventional colposcopy alone.
Healthcare setting	Colposcopy services in the NHS cervical screening programme.
Outcomes	Intermediate measures for consideration may include:

	• Diagnostic accuracy including sensitivity, specificity and predictive values. • Test failure rates. • Number of biopsies taken and diagnostic yield. • Number of treatments and treatment type. • Number of 'see and treats'. • Duration of colposcopy examination. • Number of people discharged from colposcopy.
	Clinical outcomes for consideration may include: • Morbidity and mortality associated with treatment and biopsies. • Morbidity and mortality associated with cervical cancer.
	Patient-reported outcomes for consideration may include: • Pain and anxiety associated with the colposcopy examination, biopsies, treatment and waiting for results. • Acceptability of the technologies and patient satisfaction. • Health-related quality of life.
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • adjunctive colposcopy technologies including the cost of the devices, software and any consumables • staff and associated training • medical costs from testing including ongoing care and follow up and histopathology • medical costs arising from adverse events including those associated with false test results and inappropriate treatment.
	The cost effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be long enough to reflect any differences in costs or outcomes between the technologies being compared.

Two care pathways are included in this assessment, referred to as human papilloma virus (HPV) triage and HPV primary screening. This reflects current practice in the NHS in England, where 2 cervical screening algorithms are in use. HPV triage refers to the algorithm used in most sites in England, where a cytology test is taken first. People with high-grade changes are referred for colposcopy and those with low-grade changes have a reflex HPV test on the residual cytology sample. People whose results are high-risk-HPV positive are referred for colposcopy. HPV primary screening refers to a pilot algorithm which is running in 5 sites. This is part of a recommendation by the UK National Screening Committee that HPV primary screening should replace HPV triage. In HPV primary screening, the same sample is taken but is first tested for high-risk HPV. People whose results are positive have a reflex cytology test on the residual sample. Those with either low- or high-grade abnormalities are referred for colposcopy. Those whose cytology results are negative are asked to come back in 12 months. Further details of these screening pathways can be found in the diagnostics assessment report starting on page 32.

The key difference between the algorithms is that a new group are referred for colposcopy under HPV primary screening. People who have 2 consecutive results that are HPV-positive and cytology-negative would be referred for colposcopy. In previous screening algorithms, in which the index test was cytology, they would have had no further testing and their HPV status would not have been known. The prevalence of high-grade disease (that is CIN 2 or worse [CIN2+[1]]), in the populations referred for colposcopy may differ between the screening algorithms.

Further details, including descriptions of the interventions, comparators, care pathway and outcomes can be found in the final scope.

[1] CIN2 or worse includes CIN2, CIN3, CGIN (cervical glandular intraepithelial neoplasia) and cancer.

2 The evidence

This section summarises data from the diagnostics assessment report compiled by the external assessment group (EAG).

2.1 Clinical effectiveness

The EAG did a systematic review of the evidence on the clinical effectiveness of the DYSIS colposcope with DYSISmap, hereafter referred to as DYSIS, and ZedScan I adjunctive colposcopy technologies. This included 3 reviews; 1 for diagnostic accuracy, 1 for clinical outcomes and 1 for implementation. Details of the systematic review can be found starting on page 32 of the diagnostics assessment report.

For the diagnostic accuracy review, studies were included if they reported a prospective cohort in which the index test or their prototypes (DYSIS or ZedScan I done in addition to colposcopy) and reference standard (histopathology) were done independently, and contained enough data to allow diagnostic accuracy estimates to be calculated. For the effectiveness and implementation reviews, studies were included if they reported an observational or experimental study in which DYSIS or ZedScan I, or their prototypes, were used in addition to colposcopy. Details of the inclusion and exclusion criteria can be found starting on page 34 of the diagnostics assessment report. All studies included in the diagnostic accuracy review were appraised using the QUADAS-2 tool and studies in the implementation review using guidance from Burns et al. (2008) and the Centre for Evidence Based Management (2014). In total, 12 studies were included: 11 in the diagnostic accuracy review, 3 in the review of clinical outcomes, and 5 in the review of implementation. Most studies were reported in more than 1 paper or abstract.

Evidence on diagnostic accuracy

Of the 11 studies included in the diagnostic accuracy review, 9 reported data for DYSIS, 2 of which were included in NICE's diagnostics guidance on

adjunctive colposcopy technologies (Louwers et al. 2011 and Soutter et al. 2009), and 2 reported data for ZedScan I and a prototype. All studies were done in hospital-based colposcopy clinics, and 6 were multi-centre studies. Five studies included at least 1 centre in England. Most of the participants in the studies were referred for colposcopy because of an abnormal screening result. Tidy et al. (in press) was done in 1 of the human papilloma virus (HPV) primary screening pilot sites. Founta et al. (unpublished) included only people referred for colposcopy after a test of cure, that is people whose cytology or HPV test results were abnormal around 6 months after treatment for cervical intraepithelial neoplasia (CIN).

Of the 9 DYSIS studies, 1 was considered to be at a low risk of bias and the other 8 at a high risk of bias. Both ZedScan studies (1 on ZedScan I and 1 on a prototype) were considered to be at a high risk of bias. The main source of bias in the studies was verification bias which arose because biopsies were not taken to confirm the absence of disease when no abnormalities were identified by the colposcopist. Concerns about generalisability of the results of the ZedScan studies were highlighted because the studies were done in a centre where the colposcopists were highly experienced in using the technology.

Meta-analyses were done for the diagnostic accuracy of DYSIS. Two studies were excluded from these analyses because they only reported data for subgroups and 1 was included in a narrative analysis only. The analyses assume that the DYSIS video colposcopy (without the DYSISmap), the comparator in the DYSIS studies, is equivalent in diagnostic accuracy, to binocular colposcopy (used in the ZedScan studies and in routine NHS practice). The threshold used to determine a positive result was CIN2+. No meta-analysis was done for the ZedScan studies.

Accuracy of DYSIS

The pooled results from each of the meta-analyses are summarised below in table 2. Three different analyses were done. The first meta-analysed

sensitivity and specificity separately and the results were given as forest plots. Substantial heterogeneity was found; all but 1 of the forest plots had an I^2 value of above 60%. The second analysis used a bivariate hierarchical model which accounted for the correlation between sensitivity and specificity and the third analysis used a regression model which accounted for both correlation between sensitivity and specificity, and between test results within studies. Full details can be found starting on page 64 of the diagnostics assessment report.

A sensitivity analysis was done for the logistic regression model which excluded Roensbo et al. (2015) because this study did not assess DYSIS in addition to colposcopy directly, but recorded whether a colposcopist agreed or disagreed with the DYSISmap. To examine the impact of verification bias, results were also given stratified by the number of biopsies taken in the studies when both DYSIS and colposcopy did not identify any areas of abnormality.

The results of the meta-analyses suggest that compared with colposcopy alone, DYSIS in addition to colposcopy improves sensitivity for detecting CIN2+, although this is associated with a reduction in specificity. However, the results of the logistic regression model show a significant difference in specificity between DYSIS and colposcopy (difference in log odds 1.33, $p<0.0001$), but no significant difference in diagnostic odds ratio[2] (difference in log odds 0.04, $p=0.84$). This suggests that DYSIS increases the number of biopsies taken but does not improve diagnostic accuracy when compared with colposcopy. The results of the sensitivity analyses designed to explore verification bias in people with negative DYSIS and colposcopy examinations

2 The ratio of the odds of the examination being positive if a person has CIN2 or worse relative to the odds of the examination being positive if a person does not have CIN2 or worse. A test with a diagnostic odds ratio of more than 1 suggests that the test is useful and shows some discrimination between those who have and do not have the condition; the higher the ratio the better the test. A ratio of 1 means that there is equal chance of having a positive test result regardless of the presence of the condition of interest.

suggested that sensitivity and specificity estimates decline as the number of random biopsies taken increases.

An additional 5 studies were included in a separate narrative analysis, which confirmed the results of the meta-analyses, that is DYSIS improves sensitivity but reduces specificity when compared with colposcopy. There was no clear evidence that DYSIS improved the detection of cervical cancer. Full details of these studies can be found starting on page 83 of the diagnostics assessment report.

Table 2 Summary accuracy estimates from DYSIS studies

Analysis	Technology (number of studies)	Summary estimates				
		Sensitivity (95% CI)	**Specificity (95%CI)**	**PPV (95%CI)**	**NPV (95%CI)**	**DOR (95%CI)**
Forest plots of diagnostic accuracy	Colposcopy (6 studies)[a]	58.40% (50.31% to 66.50%)	86.46% (81.26% to 91.66%)	55.78% (47.54% to 64.03%)	86.70% (80.17% to 93.22%)	9.73 (5.39 to 17.54)
	DYSISmap alone (3 studies)[b]	59.18% (33.10% to 85.26%)	81.64% (71.25% to 92.04%)	51.45% (37.19% to 65.72%)	81.63% (62.37% to 100%)	7.04 (1.69 to 29.25)
	DYSISmap + colposcopy (6 studies)[a]	81.21% (77.35% to 85.07%)	70.06% (60.31% to 79.82%)	43.60% (33.12% to 54.07%)	92.20% (88.06% to 96.34%)	10.27 (5.71 to 18.46)
Hierarchical bivariate analysis	Colposcopy (6 studies)[a]	57.74% (49.7% to 63.4%)	87.34% (79.7% to 92.4%)	-	-	-
	DYSISmap + colposcopy (6 studies)[a]	80.97% (76.0% to 85.1%)	70.90% (60.8% to 79.3%)	-	-	-
Logistic regression model	Colposcopy (6 studies)[a]	57.91% (47.2% to 67.9%)	87.41% (81.7% to 91.5%)	-	-	-
	DYSISmap + colposcopy (6 studies)[a]	81.25% (72.2 to 87.9%)	70.40% (59.4% to 79.5%)	-	-	-
Sensitivity analyses						
Logistic regression model (excluding	Colposcopy (5 studies)[c]	56.4% (47.5% to 64.9%)	90.2% (86.3 to 93.1%)	-	-	-
	DYSISmap + colposcopy	82.9%	72.9%	-	-	-

Roensbo et al. 2015)	(5 studies)[c]	(75.0% to 88.7%)	(63.3% to 80.7%)			
Studies with no biopsies in negative examinations	Colposcopy (3 studies)[d]	66.11% (40.89% to 83.33%)	92.18% 90.23% to 94.13%)	-	-	-
	DYSISmap + colposcopy (3 studies)[d]	86.11% (79.6% to 92.7%)	73.61% (50.0% to 97.2%)	-	-	-
Studies with 1 random biopsy in negative examinations	Colposcopy (Louwers et al. 2011, Soutter et al. 2009)	50.27% (43.0% to 57.5%)	86.22% (79.1% to 93.3%)	-	-	-
	DYSISmap + colposcopy (Louwers et al. 2011, Soutter et al. 2009)	78.7% (72.6% to 85.6%)	70.02% 57.9% to 82.2%)	-	-	-
Studies with multiple random biopsies in negative examinations	Colposcopy (Roensbo et al. 2015)	67.65% (56.5% to 78.8%)	67.25% 60.2% to 74.3%)	-	-	-
	DYSISmap + colposcopy (Roensbo et al. 2015)	75.0% (64.7% to 85.3%)	57.31% (49.9% to 64.7%)	-	-	-
Abbreviations: 95%CI 95% confidence interval; DOR diagnostic odds ratio; NPV negative predictive value; PPV positive predictive value.						
[a]: Budithi et al. (in press), Coronado et al. (2016), Louwers et al.(2011), Roensbo et al. (2015), Salter et al. (2016) and Soutter et al. (2009); [b]: Coronado et al. (2016), Louwers et al. (2011) and Roensbo et al. (2015); [c]: Budithi et al. (in press), Coronado et al. (2016), Louwers et al.(2011), Salter et al. (2016) and Soutter et al. (2009); [d]: Budithi et al. (in press), Coronado et al. (2016) and Salter et al. (2016)						

Accuracy of ZedScan I

Two studies were included in a narrative analysis, 1 included the current version (ZedScan I) and the other a third generation prototype. The results are shown below in table 3. Tidy et al. (in press) provides results for the current version of the device, but did not show data for colposcopy alone. The results of the studies suggest that ZedScan, when used as well as colposcopy [redacted] than colposcopy alone depending on the threshold used, but when a regression model was fitted to Tidy et al. (2013) there was no statistically significant difference (difference in log diagnostic accuracy 0.488, p=0.078).

Further data on the ZedScan I were available in 2 sub-studies of Tidy et al. (in press). A conference abstract reported that the performance of the technology [redacted]

McDonald et al. (2017) evaluated the accuracy of ZedScan I in patients with known high-risk-HPV genotypes and compared its performance between those with HPV 16 and those with other high-risk genotypes. The sensitivity of ZedScan I was high (100%) regardless of genotype but the sensitivity of colposcopy was higher in the HPV 16 group (86.9%) than in the other high-risk genotypes group (79.7%). Full details of these studies can be found starting on page 85 of the diagnostics assessment report.

Table 3 Accuracy of ZedScan I

Study	Colposcopy cut-off	Colposcopy alone		ZedScan cut-off	ZedScan + Colposcopy	
		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)
Tidy et al. (in press)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tidy et al. (2013) – prototype device	Colposcopic impression	73.6% (64.3% to 82.8%)	83.5% (76.5% to 90.5%)	1.321	73.6% (64.3% to 82.8%)	90.8% (85.4% to 96.2%)
				1.083	78.2% (69.5% to 86.8%)	83.5% (76.5% to 90.5%)
				1.568	62.1% (51.9% to 72.3%)	95.4% (91.5% to 99.3%)
	Disease present	88.5% (81.8% to 95.2%)	38.5% (29.4% to 47.7%)	0.768	88.5% (81.8% to 95.2%)	65.2% (56.2% to 74.1%)
				0.390	96.6% (92.7% to 100%)	38.5% (29.4% to 47.7%)
				0.568	92.0% (86.2% to 97.7%)	51.4% (42% to 60.8%)

Disease present = colposcopy was considered positive if at least 1 measurement point was suggested for biopsy, colposcopic impression = colposcopy was considered positive if it was judged that high-grade CIN was present.

[a] includes a HPV primary screening population

Test positive rates

Test positive rates ranged from 21.22% to 55.51% for DYSISmap plus colposcopy and from 13.77% to 42.68% for colposcopy alone in 6 DYSIS studies (Budithi et al. in press, Coronado et al. 2016, Louwers et al. 2011, Roensbo et al. 2015, Salter et al. 2016 and Souter et al. 2009). In each study the test positive rate was always higher for DYSISmap plus colposcopy than for colposcopy alone.

Test positive rates ranged from 30.20% to 77.04%, depending on the cut-off used in the 2 ZedScan studies (Tidy et al. 2013, Tidy et al. in press). Test positive rates for colposcopy were 41.84% when colposcopic impression was used as a cut-off and 73.47% when disease present was used as a cut-off (Tidy et al. 2013).

Test failure rates

Test failure rates with DYSIS were reported in 6 studies and ranged from [redacted] to 31.4%. The highest failure rate was reported by Soutter et al. (2009) which included a prototype version of the system and had problems with unsatisfactory view and faulty acetic acid applicators. Failure rates for ZedScan were reported in 2 studies, [redacted] (Zedscan I) and 13.6% (prototype) (Tidy et al. in press and Tidy et al. 2013).

Diagnostic and treatment biopsy rates

All included diagnostic accuracy studies reported some data on the number of diagnostic and treatment biopsies taken, but there were not enough details to assess whether the adjunctive technologies had a substantial effect on this. Full details of this analysis can be found starting on page 91 of the diagnostics assessment report.

Subgroup analyses

<u>High-grade and low-grade cytology referrals:</u> When data were reported for low-grade and high-grade referrals, colposcopy appeared to be less sensitive

for detecting CIN2 or worse in low-grade referrals. No differences in sensitivity were seen for DYSIS and ZedScan I.

High-risk-HPV: There was not enough data to determine whether the accuracy of any of the technologies differed between people with and without high-risk HPV.

Test of cure: Data from Founta et al. (unpublished) were included in the analysis. This showed a sensitivity of 0% (95%CI 0 to 53%) and a specificity of 94.0% (95% CI 89.35% to 98.65%) for colposcopy, and a sensitivity of 80.0% (95% CI 44.94% to 100%) and a specificity of 64.0% (95% CI 54.59% to 73.41%) for DYSIS in a test of cure population. The accuracy of colposcopy is substantially different in this study compared with the summary estimates provided in the meta-analyses for all colposcopy referrals.

Evidence on clinical outcomes

Three studies reported data on adverse events. In a ZedScan prototype study, 1 patient felt unwell after the examination and 2 patients experienced issues with bleeding after biopsies. Two DYSIS studies reported no adverse events.

No data related to morbidity and mortality associated with treatment and biopsies done during colposcopy were found and no data on health-related quality of life were found.

Two systematic reviews of adverse outcomes of CIN treatment were found. Kyrgiou et al. (2015) focussed on fertility and early pregnancy outcomes (less than 24 weeks gestation) and reported that women who have been treated for CIN were at increased risk of miscarriage in the second trimester of pregnancy (relative risk 2.60, 95%CI 1.45 to 4.67). Kyrgiou et al. (2016) focussed on obstetric (more than 24 weeks gestation) and neonatal outcomes and reported that patients who were treated with a large loop excision of the transformation zone (LLETZ) were at increased risk of giving birth prematurely

(relative risk 1.56, 95%CI 1.36 to 1.79), with the risk increasing as the depth of the excision increases.

Evidence on implementation

Five studies were included in the implementation review. Of these, 3 were based in the UK (Lowe et al. 2016, Palmer et al. 2016 and Budithi et al. in press), 1 in Spain (Coronado et al. 2014) and 1 in the Netherlands (Louwers et al. 2015). None of the studies used validated questionnaires.

Patient and clinician satisfaction

Lowe et al. (2016) surveyed 763 patients in 4 NHS hospitals that were using DYSIS. Two questionnaires were available: 1 for patients having their first colposcopy and 1 for people who had previously had a colposcopy; the number of respondents per questionnaire was not reported. Participants reported that the examination did not take longer than their previous smear test or colposcopy and that anxiety was reduced during and after DYSIS examinations compared with during previous examinations.

Louwers et al. (2015) gave a patient satisfaction questionnaire to 239 people who had a DYSIS examination. Results showed that 93.9% of participants agreed or strongly agreed to have colposcopy with DYSIS if it helped locate CIN, 29.5% agreed or strongly agreed that DYSIS was less comfortable than a cervical smear, 16.5% reported that DYSIS made them feel nervous during the examination, and 6.5% thought that an examination with DYSIS took too long.

Budithi et al. (2017) gave questionnaires to both patients and colposcopists in 5 colposcopy clinics in Wales; 68 patients and 45 colposcopists responded. Results from patients showed that: 86% agreed or strongly agreed that the DYSIS images helped their understanding and were reassuring, 52% believed DYSIS to be more accurate than their previous colposcopy, 4% thought that DYSIS lasted too long compared with previous colposcopies and 13% found it less comfortable. Of the colposcopists who filled in the questionnaire: 96%

agreed or strongly agreed that they were confident about colposcopy and their decision making in selecting biopsy sites, but 48% went on to agree that DYSISmap impacted their decisions in selecting biopsy sites, 58% said they were able to identify additional sites with DYSISmap, and 55% agreed or strongly agreed that DYSISmap improved their colposcopic examination.

Coronado et al. (2014) surveyed 63 colposcopists with different levels of experience. A retrospective review of 50 colposcopy and DYSISmap images was also done. This found that correct diagnosis was more frequent with DYSIS than with conventional colposcopy for colposcopists with low and medium levels of experience. There was no difference for highly experienced colposcopists. All groups agreed that DYSIS was better at directing diagnosis and provides more information than conventional colposcopy.

Training requirements

One study, done in a colposcopy clinic in Sheffield reported the time needed to train colposcopists using a ZedScan prototype for the first time. It found that 5 to 10 minutes extra time was needed for the first training period, and that after examining 10 to 20 patients the colposcopists were able to finish the ZedScan measurements in 2 to 3 minutes.

2.2 Cost effectiveness

The EAG did a search to identify existing studies investigating the cost effectiveness of DYSIS and ZedScan I. The EAG also constructed a de novo economic model to assess the cost effectiveness of the 2 technologies in both a population referred for colposcopy under the HPV triage screening algorithm and under the HPV primary screening pilot site algorithm.

Systematic review of cost-effectiveness evidence

Two relevant economic evaluations were identified; 1 (Wade et al. 2013) provided results for DYSIS compared with colposcopy over a life-time time horizon and (Whyte et al. 2013) provided results for a ZedScan prototype

compared with colposcopy over a 3 year time horizon. Wade et al. (2013) was produced for NICE's diagnostics guidance on adjunctive colposcopy technologies and found that DYSIS dominated (that is, cost less and was more effective than) colposcopy. Whyte et al. (2013) reported lower costs associated with the use of ZedScan because it was found to reduce rates of overtreatment and reduce the number of follow-up appointments needed for people with CIN1. This study used accuracy data from a prototype version with higher specificity and lower sensitivity than the commercial device (ZedScan I). Neither of the studies fully addressed the decision problem. Full details of these studies can be found starting on page 106 of the diagnostics assessment report.

Economic analysis

The EAG developed a de novo economic model designed to assess the cost effectiveness of DYSIS and ZedScan I used in addition to colposcopy in both a HPV triage and a HPV primary screening setting. The analyses took the perspective of the NHS and Personal Social Services and had a 60 year (life-time) time horizon. All costs and effects were discounted at a rate of 3.5%.

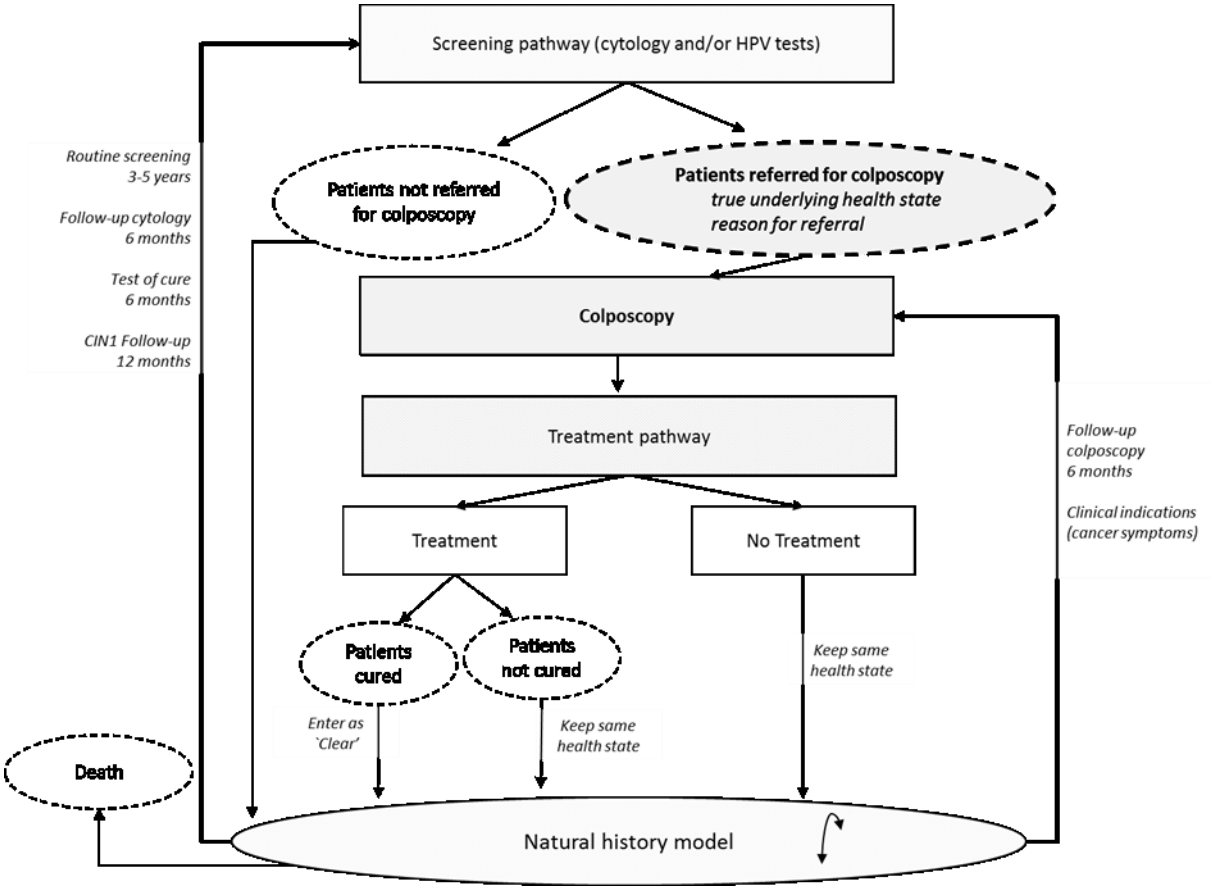
Model structure

A patient-level state-transition model with a 6 month cycle time was constructed using TreeAge Pro (2016) software. The model included 500,000 simulations to ensure that first-order uncertainty was adequately captured, that is, variability in the simulated experiences between patients. The model incorporates both screening and treatment pathways, a sub-model which simulates the natural history of CIN and cervical cancer, and a sub-model for women treated for CIN which simulates adverse obstetric outcomes. The adverse obstetric outcome model captures the costs and quality-adjusted life year (QALY) decrements associated with initial management and the increased probability of neonatal mortality and QALY decrements associated with higher risks of disability amongst infants born pre-term. The natural

history model was adapted from Kulasingam et al. (2013) with invasive cancer parameters taken from Campos et al. (2014).

At the beginning of the first cycle each patient is referred for colposcopy and treated if necessary, before entering the natural history model. In subsequent cycles, the patient can follow 1 of 4 screening and treatment pathways: no screening, colposcopy referral, routine screening or a follow-up pathway for those who were previously treated, unless they died in the previous cycle. Every pathway ends with the patient entering the natural history model. Further details of each of the main elements of the model can be found starting on page 130 of the diagnostics assessment report. Figure 1 shows the interactions between each main component of the model. Full schematics of the model can be found starting on page 136 of the diagnostics assessment report.

Figure 1 Interactions between model components



The model was implemented using random walk[3] and for each patient it simulated the occurrence of the following uncertain events: disease progression, diagnostic results or treatment outcomes. The characteristics which determined the associated events and transitions for each individual in the model were as follows:

- age
- health state (clear, HPV, CIN1, CIN2/3, cancer)
- reason for referral for colposcopy (high grade or low grade)

[3] A series of random numbers which determine the next transition between events for each patient

- next scheduled screening (routine call, 6 months cytology, 6 months colposcopy, test of cure, CIN1 follow up)
- time elapsed since last screening
- type of clinic visited ('see and treat' or 'watchful waiting').

The modelled pathways for HPV triage were based on those outlined in NHS cervical screening programme (NHSCSP) document 20 'colposcopy and programme management' and for HPV primary screening on the testing algorithms used in the NHSCSP's pilot sites. Further details of these can be found starting on page 133 of the diagnostics assessment report.

Model inputs

The model was populated with data from the clinical-effectiveness review, published literature and expert opinion. Full details of the model inputs can be found starting on page 124 of the diagnostics assessment report.

Diagnostic accuracy estimates

The diagnostic accuracy estimates used in the model for DYSIS, ZedScan I and colposcopy are shown in table 4. These estimates were thought to be the most robust from the review of diagnostic accuracy.

Table 4 Accuracy estimates used in the model

Technology (source)	Sensitivity (95% CI)	Specificity (95%CI)
Colposcopy alone (regression model)	57.91% (47.2% to 67.9%)	87.41% (81.7% to 91.5%)
DYSIS (regression model)	81.25% (72.2% to 87.9%)	70.40% (59.4% to 79.5%)
ZedScan I (Tidy et al. in press)	[redacted]	[redacted]

The performance of cytology was modelled using data from Hadwin et al. (2008) and from the NHSCSP statistical bulletin (2015/16). This was applied to cytology in both the HPV triage and HPV primary screening scenarios. The

diagnostic accuracy of HPV testing in HPV triage was modelled using data from the TOMBOLA study (Cotton et al. 2010) and in HPV primary screening from the ARTISTIC study (Kitchener et al. 2014). Full details of these inputs can be found starting on page 142 of the diagnostics assessment report.

Underlying health states and reasons for referral

In the model, people referred for colposcopy have 2 initial characteristics; a true underlying health state (clear, HPV, CIN1, CIN2/3 or cancer) and a reason for referral (low grade or high grade). These distributions were taken from the NHSCSP statistical bulletin (2015/16) for HPV triage and from unpublished data provided by the NHSCSP pilot sites for HPV primary screening. Full details of these inputs can be found starting on page 144 of the diagnostics assessment report.

Treatment probabilities

Heterogeneity in treatment decisions after a positive colposcopy was modelled using 2 different types of clinic; a 'watchful waiting' clinic or a 'see and treat' clinic. The probability of treatment failure after an excisional biopsy was taken from Ghaem-Maghami et al. (2011) and ranged from 4.9% for CIN1 to 10.3% for CIN3. The probability of adverse obstetric outcomes after treatment was estimated by applying the relative risk of pre-term birth (1.56) from Kyrgiou et al. (2016) to the probability of pre-term birth for untreated women reported in NICE's guideline on preterm labour and birth (7.3%). This gave an excess risk of pre-term birth after LLETZ treatment of 4.09%. Full details of these inputs can be found starting on page 146 of the diagnostics assessment report.

Costs

The average cost per patient of using the technologies was calculated using information from companies and clinical experts. The costs include the capital cost of the technologies (annuitised over 15 years for a colposcope and 5 years for DYSIS and ZedScan I), annual maintenance costs and

consumable costs. To calculate the average cost per procedure, it was assumed that 1,229 patients per year were seen. The following costs per patient were assumed:

- Colposcopy: £3.75
- DYSIS: £9.24
- ZedScan I: £30.52

Biopsy and treatment costs were taken from NHS reference costs and the cost of a cytology and HPV test were taken from the TOMBOLA study and inflated to 2016 prices. The costs used in the model are shown in table 5.

Table 5 Treatment and procedure costs

Treatment	Device	Cost per treatment
Colposcopy examination only	Colposcopy	£175
	DYSIS	£180.49
	ZedScan I	£205.52
Diagnostic biopsy		£47
LLETZ		£63
Cytology test		£37.19
HPV test		£29.66

Cancer treatment costs were taken from Martin-Hirsch et al. (2007) and costs associated with adverse obstetric outcomes were taken from Lomas et al. (2016) and inflated to 2016 prices. It was assumed that a pre-term birth costs £24,610 which takes into account initial inpatient neonatal care and ongoing costs over the first 18 years of life. Full details of the costs used in the model can be found starting on page 151 of the diagnostics assessment report.

Health-related quality of life and QALY decrements

Health-related quality-of-life estimates were taken from the published literature. The disutilities associated with screening, diagnosis and treatment of CIN were taken from Simonella and Canfell (2014) and are shown below in table 6. Age and gender specific utilities from Kind et al. (1999) were applied

to the HPV, CIN1 and CIN2/3 asymptomatic health states. Disutilities associated with cervical cancer were taken from Goldie et al. (2004) and a QALY decrement of 1.3 was applied for pre-term birth (Lomas et al. 2016). Full details of the health-related quality-of-life inputs can be found starting on page 156 of the diagnostics assessment report.

Table 6 Disutilities for screening, diagnosis and treatment

Screening event	QALY decrement
Negative cytology or HPV	0.0062
False positive referral for colposcopy	0.0276
Diagnosed CIN1	0.0276
Treatment of CIN	0.0296

Base-case results

For the purposes of decision making, the incremental cost-effectiveness ratios (ICERs), that is, the cost or saving per QALY gained or lost, will be considered. The following assumptions were applied in the base-case analysis:

- Diagnostic accuracy estimates for both colposcopy and the adjunctive technologies were based on a cut-off of CIN2 or worse.
- The probability of a positive colposcopy result was:
  - identical for people with clear, HPV and CIN1 results
  - identical for people with CIN2/3 and invasive cancer.
- The choice between a ‘see and treat’ clinic and a ‘watchful waiting’ clinic was independent from diagnostic accuracy.
- Biopsy and histopathology (the reference standard) were 100% accurate
  - ‘watchful waiting’ never resulted in inappropriate treatment.
- Excision at first colposcopy appointment was only possible for high-grade referrals with a positive colposcopy result
  - low specificity lead to overtreatment in ‘see and treat’ clinics.

- For low-grade referrals, CIN2 was confirmed by diagnostic biopsy before treatment.
- CIN1 lesions were not treated and patients have a 12 month follow up screening in the community.
- Women treated for CIN remained at risk of pre-term birth (birth before 37 weeks gestation) for each year post-treatment up to the age of 45.
- When cancer was detected treatment was given appropriate to the stage and an excess risk of mortality was applied for 5 years and decreased according to time since diagnosis.
- Examinations with DYSIS and ZedScan I were equivalent in duration to a standard colposcopy examination.
- ZedScan I was used for diagnostic colposcopies only.

The EAG gave 2 base cases; one for HPV triage and one for HPV primary screening. The results of each of the base cases are presented according to the type of clinic and are shown below in tables 7 to 10. The results of the HPV triage base case suggest that both technologies dominate standard colposcopy in 'see and treat' clinics (that is, they cost less and are more effective). Also, results suggests that ZedScan I always costs more but is more effective than DYSIS. In 'watchful waiting' clinics, DYSIS dominates standard colposcopy for low-grade referrals and for all referrals combined, but had an ICER of £675 per QALY gained for high-grade referrals. ZedScan I always costs more but is more effective than standard colposcopy. The results of the HPV primary screening base case were similar to the HPV triage base case. Full results from the base-case analyses can be found starting on page 165 of the diagnostics assessment report.

Table 7 HPV triage base case –'see and treat' clinics

	Strategy	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER
DYSIS versus colposcopy						
All referrals	Colposcopy alone	903.28	19.16500			
	DYSIS	872.34	19.18516	-30.94	0.02016	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	DYSIS	770.65	19.18794	-23.33	0.02464	Dominant
HG referrals	Colposcopy alone	1,139.13	19.16122			
	DYSIS	1,091.43	19.17156	-47.70	0.01034	Dominant
ZedScan I versus colposcopy						
All referrals	Colposcopy alone	903.28	19.16500			
	ZedScan I	885.91	19.19901	-17.37	0.03401	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	ZedScan I	789.30	19.20307	-4.68	0.03978	Dominant
HG referrals	Colposcopy alone	1,139.13	19.16122			
	ZedScan I	1,091.97	19.17651	-47.16	0.01529	Dominant
ZedScan I versus DYSIS						
All referrals	DYSIS	872.34	19.18516			
	ZedScan I	885.91	19.19901	13.57	0.01385	980
LG referrals	DYSIS	770.65	19.18794			
	ZedScan I	789.30	19.20307	18.65	0.01514	1232
HG referrals	DYSIS	1,091.43	19.17156			
	ZedScan I	1,091.97	19.17651	0.54	0.00495	109
LG: low grade, HG: high grade						

Table 8 HPV triage base case – 'watchful waiting' clinics

	Strategy	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER
DYSIS versus colposcopy						
All referrals	Colposcopy alone	953.02	19.16286			
	DYSIS	941.33	19.18194	-11.69	0.01908	Dominant
LG referrals	Colposcopy alone	812.85	19.16283			
	DYSIS	799.47	19.18601	-13.38	0.02318	Dominant
HG referrals	Colposcopy alone	1,252.07	19.16008			
	DYSIS	1,255.93	19.16580	3.85	0.00571	675
ZedScan I versus colposcopy						
All referrals	Colposcopy alone	953.02	19.16286			
	ZedScan I	965.87	19.19363	12.85	0.03078	418
LG referrals	Colposcopy alone	812.85	19.16283			
	ZedScan I	823.19	19.20082	10.34	0.03799	272
HG referrals	Colposcopy alone	1,252.07	19.16008			
	ZedScan I	1,288.82	19.16911	36.75	0.00903	4070
ZedScan I versus DYSIS						
All referrals	DYSIS	941.33	19.18194			
	ZedScan I	965.87	19.19363	24.54	0.01170	2098
LG referrals	DYSIS	799.47	19.18601			
	ZedScan I	823.19	19.20082	23.72	0.01481	1601
HG referrals	DYSIS	1,255.93	19.16580			
	ZedScan I	1,288.82	19.16911	32.89	0.00332	9918
LG: low grade, HG: high grade						

Table 9 HPV primary screening base case – 'see and treat' clinics

	Strategy	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER
DYSIS versus colposcopy						
All referrals	Colposcopy alone	850.08	19.17506			
	DYSIS	825.46	19.19120	-24.62	0.01614	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	DYSIS	715.46	19.20787	-16.87	0.01779	Dominant
HG referrals	Colposcopy alone	1,126.93	19.16192			
	DYSIS	1,079.83	19.16774	-47.11	0.00581	Dominant
ZedScan I versus colposcopy						
All referrals	Colposcopy alone	850.08	19.17506			
	ZedScan I	844.41	19.20206	-5.67	0.02700	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	ZedScan I	744.85	19.22007	12.52	0.03000	417
HG referrals	Colposcopy alone	1,126.93	19.16192			
	ZedScan I	1,082.27	19.17347	-44.66	0.01155	Dominant
ZedScan I versus DYSIS						
All referrals	DYSIS	825.46	19.19120			
	ZedScan I	844.41	19.20206	18.95	0.01085	1746
LG referrals	DYSIS	715.46	19.20787			
	ZedScan I	744.85	19.22007	29.39	0.01220	2408
HG referrals	DYSIS	1,079.83	19.16774			
	ZedScan I	1,082.27	19.17347	2.45	0.00574	426
LG: low grade, HG: high grade						

Table 10 HPV primary screening base case – 'watchful waiting' clinics

	Strategy	Cost (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER
DYSIS versus colposcopy						
All referrals	Colposcopy alone	894.41	19.17511			
	DYSIS	889.04	19.18937	-5.37	0.01426	Dominant
LG referrals	Colposcopy alone	748.86	19.18496			
	DYSIS	738.10	19.20646	-10.77	0.02150	Dominant
HG referrals	Colposcopy alone	1,236.94	19.15863			
	DYSIS	1,240.99	19.16234	4.06	0.00371	1095
ZedScan I versus colposcopy						
All referrals	Colposcopy alone	894.41	19.17511			
	ZedScan I	918.78	19.19977	24.37	0.02466	988
LG referrals	Colposcopy alone	748.86	19.18496			
	ZedScan I	770.26	19.21984	21.40	0.03487	614
HG referrals	Colposcopy alone	1,236.94	19.15863			
	ZedScan I	1,276.58	19.16668	39.64	0.00805	4922
ZedScan I versus DYSIS						
All referrals	DYSIS	889.04	19.18937			
	ZedScan I	918.78	19.19977	29.74	0.01040	2860
LG referrals	DYSIS	738.10	19.20646			
	ZedScan I	770.26	19.21984	32.16	0.01338	2404
HG referrals	DYSIS	1,240.99	19.16234			
	ZedScan I	1,276.58	19.16668	35.58	0.00434	8190
LG: low grade, HG: high grade						

The number of treatments, biopsies and missed disease in each of the base cases is shown below in table 11. This shows that because of their increased sensitivity, the adjunctive technologies are associated with less missed disease and so less cancers. However, they also have reduced specificity and result in more unnecessary diagnostic biopsies and treatments (except 'watchful waiting' clinics).

Table 11 secondary outcomes per 1,000 people referred for colposcopy (all referrals)

Clinic	Strategy	Missed CIN2+	Cancers	LLETZ	Unnecessary LLETZ	Unnecessary diagnostic biopsy
HPV triage						
'See and treat'	Colposcopy	69	43	466	27	139
	DYSIS	30	34	501	61	229
	ZedScan I	3	29	524	82	291
'Watchful waiting'	Colposcopy	69	44	449	0	137
	DYSIS	30	37	465	0	260
	ZedScan I	3	32	477	0	347
HPV primary screening						
'See and treat'	Colposcopy	82	33	446	22	164
	DYSIS	34	25	478	50	296
	ZedScan I	4	20	498	68	386
'Watchful waiting'	Colposcopy	82	34	432	0	172
	DYSIS	34	27	450	0	316
	ZedScan I	4	22	460	0	417
CIN2+: cervical intraepithelial neoplasia grade 2 or worse, LLETZ: large loop excision of the transformation zone						

Analysis of alternative scenarios

The following scenario analyses were done to explore the impact of alternative structural assumptions:

- Time horizon restricted to 1 screening interval (3 years).
- Adverse obstetric outcomes excluded.
- ZedScan I used in both diagnostic and treatment colposcopies.

When the time horizon was restricted to 3 years colposcopy dominated (it cost less and was more effective than) both DYSIS and ZedScan I under most scenarios except for high-grade referrals in 'see and treat' clinics. In this scenario, DYSIS had an ICER of £236,692 saved per QALY lost and ZedScan I had an ICER of £84,045 saved per QALY lost under HPV triage. Under HPV primary screening, the respective ICERs were £250,587 saved per QALY lost

for DYSIS and £110,371 saved per QALY lost for ZedScan I. Colposcopy generally dominated because its higher specificity resulted in fewer treatments, but people with untreated CIN (false negatives) did not go on to develop cancer within the 3 year time horizon. The results of the model did not change substantially in the other scenario analyses. Full details of the scenario analyses can be found starting on page 184 of the diagnostics assessment report.

Sensitivity analyses

The following inputs were changed in sensitivity analysis to explore the impact of parameter uncertainty:

- diagnostic accuracy
- costs of technologies
- costs of treatment and biopsies
- characteristics of the population referred for colposcopy under HPV primary screening.

When the accuracy of colposcopy relative to ZedScan I was taken from Tidy et al. (2013) the incremental costs associated with ZedScan I compared with colposcopy increased, while the QALYs decreased. Under these assumptions ZedScan became less cost effective than in the base case and it no longer dominated colposcopy in ‘see and treat’ clinics. Its highest ICER was £24,686 per QALY gained for high-grade referrals in HPV primary screening ‘watchful waiting’ clinics.

The DYSIS results were sensitive to assumptions around reduced throughput and a consequent increase in cost per test because of its higher purchase price. When it was assumed that only 614 patients per year were seen, it no longer dominated colposcopy in HPV primary screening ‘watchful waiting’ clinics.

The ZedScan results were sensitive to changes in the cost of diagnostic and treatment biopsies because of its increased sensitivity and lower specificity compared with colposcopy. When the cost of a diagnostic biopsy was increased to £102.72 and a treatment biopsy (LLETZ) to £490.89, ZedScan no longer dominated colposcopy for low-grade referrals and all referrals combined. None of the other sensitivity analyses changed the results substantially. Full details of the sensitivity analyses can be found starting on page 176 of the diagnostics assessment report.

3 Summary

Data suggests that the adjunctive colposcopy technologies are associated with increased sensitivity but reduced specificity when compared with standard colposcopy, particularly amongst low-grade referrals. However, only limited data were available for the ZedScan I device. The clinical value of the adjunctive technologies therefore depends on whether the value of diagnosing more cases of cervical intraepithelial neoplasia (CIN) outweighs the disadvantages that could be associated with an increased rate of biopsies and treatment. There were only limited data relating to the clinical effectiveness of both DYSIS and ZedScan I. DYSIS appeared to be well received by both clinicians and patients.

The results of the cost-effectiveness analysis were robust to many assumptions and in most scenarios the adjunctive technologies dominated standard colposcopy or had an incremental cost-effectiveness ratio (ICER) of less than £5,000 per quality-adjusted life year (QALY) gained. In indirect comparisons, ZedScan I appeared to cost more but be more effective than DYSIS. Only exploratory analyses could be done for HPV primary screening.

Both adjunctive colposcopy technologies increased the number of biopsies and treatments compared with standard colposcopy alone. In a life-time time horizon, the negative impacts of this appeared to be offset by preventing more cases of cervical cancer. But when this was reduced to 3 years and only the

shorter-term events were considered, the adjunctive technologies were dominated by standard colposcopy for all referrals.

4 Issues for consideration

Clinical effectiveness

Binocular and video colposcopy were both used as comparators in the analysis. Colposcopy in the DYSIS studies was done using video colposcopy (DYSIS colposcope without the DYSISmap) but binocular colposcopy is used in the comparative ZedScan study. Binocular colposcopy is predominantly used as standard in the UK and it is uncertain whether video colposcopy has equivalent diagnostic accuracy.

Studies from countries outside of England were included in the analyses. It is not known whether the results from these studies are applicable to clinical practice in the NHS in England because differences in screening programmes may affect the characteristics of the populations referred for colposcopy. Also, the standard of colposcopy may differ. In the included DYSIS studies, the positive predictive value for colposcopy alone was 55.8% for CIN2 or worse; the recommended positive predictive value in England is 65%.

Different versions of the systems were used in the included studies. The company states that the algorithm used in the DYSISmap is equivalent between the current version and earlier versions, but the cut-offs used by the ZedScan device differ between the commercialised version of the device (ZedScan I) and the prototype.

Only 2 studies were available to inform the diagnostic accuracy analyses for ZedScan I. One study reported results from a prototype device and the other did not report full diagnostic accuracy results for colposcopy alone.

Only limited diagnostic accuracy data were available for a HPV primary screening population, with only 1 study using ZedScan I done in this setting. It

is therefore not certain how the adjunctive technologies may perform once HPV primary screening is rolled out across England.

Not enough data were available to fully assess the impact of HPV genotype on the accuracy of the adjunctive colposcopy technologies. There was some evidence to suggest that DYSIS may have greater accuracy in people with high-risk-HPV. It is therefore uncertain how the accuracy of both the adjunctive technologies and colposcopy may differ once a fully vaccinated population start screening.

The reported accuracy values in the included studies were shown to be highly dependent on how the reference standard was implemented, that is whether biopsies were taken when colposcopy was normal, or only when an abnormality was seen. This suggests that the results are subject to verification bias because of under-diagnosis of high-grade CIN, but because this affects both the adjunctive technologies and the comparator it is likely that this may not significantly affect the validity of the relative differences in accuracy that were reported.

No data relating to clinical outcomes amongst people having colposcopy with an adjunctive technology were found. It is therefore not certain whether the increased sensitivity of the technologies leads to detection of smaller, less colposcopically apparent lesions, which may have regressed over time without treatment. Also, there were not enough data to determine whether the adjunctive technologies improve the detection of cervical cancer.

Cost effectiveness

The model does not consider conservative management of CIN2, which clinical experts have suggested is becoming more widely accepted in people with smaller lesions or in those who have not yet completed their family. The model may therefore not fully reflect current practice in terms of the number of additional treatments that are associated with the use of the adjunctive technologies.

No probabilistic sensitivity analysis was done and parameter and structural uncertainty was explored through sensitivity and scenario analyses. Although the model was robust to most of the changes investigated in this analyses, it is likely that the impact of decision uncertainty has not been fully explored.

The impact of adverse obstetric outcomes was explored in a scenario analysis. Removing the disutility associated with adverse obstetric outcomes did not appear to have a substantial effect on the model results. The results of the model may therefore appear counterintuitive to clinical practice, which aims to reduce the number of unnecessary treatments, because the technologies remain cost effective despite additional adverse obstetric outcomes.

The influence of longer-term outcomes was explored in a scenario analysis which reduced the time horizon to 3 years. This had the effect of removing penalties for lower sensitivity because people with missed CIN2 did not go on to develop cancer within the time horizon. Also, the higher specificity of standard colposcopy lead to less treatments and a reduced cost compared with the adjunctive technologies. This scenario highlights the trade-off between sensitivity and specificity and their downstream consequences.

The HPV primary screening analyses are based on both preliminary data and clinical management algorithms from the pilot sites. It is possible that further adaptations may be made to the algorithms before they are rolled out across England. Therefore, the results of these analyses should be considered exploratory.

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Older people may be more likely to have a colposcopy examination that is classed as unsatisfactory because the cervical transformation zone may not be fully visualised. Colposcopy management is likely to be different for women who are pregnant because 'watchful waiting' until after delivery may be recommended as an alternative to biopsies and treatment. Identification of cellular changes during colposcopy may also be more difficult in women who are pregnant because of changes that happen in the cervix during pregnancy. These potential issues are associated with the condition and are unlikely to be impacted on by the adjunctive technologies.

6 Implementation

Clinician confidence

Some colposcopists may have a preference for conventional colposcopy. It is important to emphasise that the technologies would be used in addition to, and not as a replacement for, conventional colposcopy because the skills and expertise of a colposcopist would still be needed to help interpret the information provided by the adjunctive technologies. This may help to overcome the view that relying on technologies to identify cervical abnormalities can lead to colposcopists becoming deskilled.

Record management

The adjunctive technologies would need to be able to integrate their databases with the colposcopy service's database. Lack of integration could result in duplication between databases which can lead to inefficiencies and the potential for incomplete records.

Capacity

Centres that currently use the adjunctive colposcopy technologies often do not have enough devices for all colposcopists to use them at the same time. This leads to some people being assessed with conventional colposcopy alone while others also have an assessment with 1 of the adjunctive technologies.

Training

After the initial training period, there may be the need for ongoing mentorship while colposcopists become familiar with using the adjunctive technologies.

7 Authors

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July 2017

Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report was prepared by the University of York:

Péron M, Llewellyn A, Moe-Byrne T, Walker S, Walton M, Harden M, Palmer S and Simmonds M (2017) Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: a systematic review with meta-analysis and economic evaluation.

B. The following organisations accepted the invitation to participate as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturer(s) of technologies included in the final scope:

- DYSIS Medical Ltd
- Zilico Ltd

Other commercial organisations:

None

Professional groups and patient/carer groups:

- British Association for Cytopathology
- British Society for Colposcopy and Cervical Pathology
- Jo's Cervical Cancer Trust
- Royal College of Pathologists

Research groups:

- Cancer Research UK

Associated guideline groups:

None

Others:

- Cervical Screening Wales
- Department of Health
- Healthcare Improvement Scotland
- Medicines and Healthcare Products Regulatory Agency
- NHS England
- Public Health England
- Welsh Government

Appendix B: Glossary of terms

Cervical intraepithelial neoplasia

Changes in the squamous cells that line the surface of the cervix. These cellular changes are often referred to as pre-cancerous changes. The cells have the potential to turn into cancer over time if left untreated, particularly those which show evidence of high-grade changes.

Cervical glandular intraepithelial neoplasia

Changes in the glandular (columnar) cells that line the inner cervical canal. Like cervical intraepithelial neoplasia, cervical glandular intraepithelial neoplasia is a pre-cancerous change, although these abnormalities do not happen as frequently.

High-risk HPV genotypes

Genotypes of HPV that are associated with the development of cervical intraepithelial neoplasia and cervical cancer. There are around 14 high-risk genotypes that can be detected using commercially available high-risk HPV tests, including types 16 and 18 which are responsible for a large proportion of cervical cancers (around 70% in the UK). Vaccination against HPV 16 and 18 is offered to girls aged 12 to 13 in the NHS childhood vaccination programme.

Human Papilloma virus (HPV)

Infection with human papillomavirus is the single most important risk factor for developing cervical cancer. Most infections are transient, but in some people they persist and may cause changes in the cells of the cervix. Only certain types of HPV known as high-risk genotypes are associated with cervical intraepithelial neoplasia and cervical cancer.

Large loop excision of the transformation zone (LLETZ)

An electro-surgical procedure which uses a thin wire loop to remove areas abnormal cells on the cervix. This is usually done with local anaesthetic in the colposcopy clinic. The area of cells removed is sent to histopathology where a

pathologist can confirm the extent of the abnormality, and if all the abnormal cells have been removed.

Punch biopsy

A procedure which removes a small sample of cells from areas of the cervix that a colposcopist believes contain an abnormality. The cells are examined by a pathologist in a laboratory and the results are used to determine whether any treatment is needed.