NICE National Institute for Health and Care Excellence

NICE guidance

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: the DYSIS colposcope with DYSISmap and the ZedScan I

HealthTech guidance
Published: 25 April 2018

www.nice.org.uk/guidance/htg467

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces MIB20, DG4 and DG32.

1 Recommendations

1.1 The Dynamic Spectral Imaging System (DYSIS) colposcope with DYSISmap shows promise and is recommended for assessing suspected cervical abnormalities in people having colposcopy. Centres using the technology should audit their outcomes (see section 5.16).

1.2 Further research is recommended on the effects of using the DYSIS colposcope with DYSISmap on clinical and patient outcomes in a human papilloma virus primary screening setting, and on patient experience (see sections 6.1 to 6.3).

More research is needed

1.3 The ZedScan I shows promise in assessing suspected cervical abnormalities, but there is currently not enough evidence to recommend its routine adoption. Further research on the effects of using the technology on clinical and patient outcomes is recommended (see sections 6.1 to 6.3). Colposcopy services that implemented the ZedScan I before this guidance was published are encouraged to take part in studies that address these research recommendations.

2 Clinical need and practice

The problem addressed

2.1 The Dynamic Spectral Imaging System (DYSIS) colposcope with DYSISmap and the ZedScan I adjunctive colposcopy technologies are intended to be used with colposcopy to help identify cervical intraepithelial neoplasia (CIN) during a colposcopy examination. CIN is a term used to describe precancerous changes in cells in the surface layer of the cervix (the cervical epithelium). Most changes arise in the transformation zone, where the endocervical canal (the internal canal of the cervix) meets the external part of the cervix. This is the area examined during standard colposcopy, and from where a sample is taken for cervical screening. Less often, abnormalities occur on the inside of the cervical canal instead of the surface. These changes are known as cervical glandular intraepithelial neoplasia.

2.2 Standard colposcopy is subjective and can be associated with both inter- and intra-observer variability, particularly with lower-grade abnormalities. It is usually done using a binocular colposcope, unless the clinic has a DYSIS colposcope that incorporates a digital (video) colposcope. The adjunctive colposcopy technologies aim to evaluate cellular changes objectively, using optical or electrical impedance spectroscopy to assess the characteristics of cervical cells.

2.3 The results provided by the technologies can help a colposcopist to decide whether further treatment or biopsies are needed, by guiding them to areas that are most likely to be abnormal. If the results do not suggest any areas of abnormality, and standard colposcopy is normal, the colposcopist can be more confident that high-grade disease is unlikely to be present. It is claimed that using the devices may result in more accurate detection of cervical abnormalities and identification of the correct sites for biopsy.

2.4 The purpose of this assessment is to evaluate the clinical and cost effectiveness of the DYSIS colposcope with DYSISmap and the ZedScan I. It is a full update of NICE's diagnostics guidance on the DYSIS colposcope with DYSISmap and the Niris Imaging System, which was published in 2012. NICE's original guidance

concluded that DYSIS was a clinically and cost-effective option compared with standard colposcopy. Since the guidance was published there have been changes to the care pathway (see sections 2.9 and 2.10) and changes to the CE-marked products. Also, the Niris Imaging System is no longer available.

The condition

Cervical intraepithelial neoplasia and cervical cancer

2.5 Cervical cancer is one of the less common cancers in the UK, largely because of the NHS cervical screening programme (NHSCSP). In 2013 there were 3,200 cases of cervical cancer in the UK (Cancer Research UK), which accounted for less than 1% of all new cases of cancer. In 2014 there were 890 deaths from cervical cancer in the UK (Cancer Research UK). The main cause of cervical cancer is persistent infection with high-risk genotypes of human papilloma virus (HPV; hereafter referred to as high-risk HPV), which causes changes in the cervical cells that can progress to cervical cancer if not treated.

2.6 CIN is classified based on the depth of abnormal cells in the surface layer of the cervix seen on a diagnostic or excisional (treatment) biopsy:

- CIN 1: one third of the thickness of the surface layer is affected
- CIN 2: two thirds of the thickness of the surface layer is affected
- CIN 3: the full thickness of the surface layer is affected.

  Grades 2 and 3, often referred to as high-grade, are usually treated to prevent possible progression to cervical cancer. But expert advice suggests that CIN 2 may be managed more conservatively in people who have smaller lesions and who have not completed their family.

The diagnostic and care pathways

Diagnosis

2.7 Precancerous changes to cells in the cervix are detected by cervical screening. People are invited, through the NHSCSP, to have cervical screening every 3 years for those aged 25 to 49 and every 5 years for those aged 50 to 64. It involves taking a sample of cells from the cervix, usually the transformation zone (see section 2.1), using a specially designed brush. The cells are preserved using liquid-based cytology kits and are sent to a cytology laboratory where they are examined under a microscope.

2.8 The criteria for reporting cervical cytology and the management protocols for results are outlined in the NHSCSP's achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology (commonly known as ABC3; 2013). Samples are graded depending on the degree of abnormality, known as dyskaryosis (changes to the nucleus of a cell), seen under the microscope. Finding dyskaryotic cells suggests the presence of CIN.

2.9 The current management protocols for cervical cytology are described in the third edition of the NHSCSP's colposcopy and programme management guidelines (2016). Currently, people with samples that show high-grade dyskaryosis or worse are referred for colposcopy. If low-grade dyskaryosis is seen, the residual cells collected during the cervical screen are used for high-risk HPV testing to determine whether a colposcopy referral is needed. This is part of the management protocol referred to as HPV triage. The HPV test helps to identify people who are at the greatest risk of having abnormalities that may need further investigation and treatment. If low-grade dyskaryosis is seen but HPV is not detected, the risk of having underlying abnormalities is low and the cellular changes are likely to resolve without further investigation or treatment.

2.10 In July 2016, the Department of Health announced its decision to begin HPV primary screening through the NHSCSP. In HPV primary screening, the sample is tested for high-risk HPV first. If the results are positive, a cytology test is routinely done on the residual sample. People 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. HPV primary screening has now

been adopted as the standard of care in several sites in England where it was piloted. Full roll out of this pathway is expected by 2019.

Treatment

2.11 Treatment for CIN aims to remove the cells either by excision or ablation. Treatment for cervical glandular intraepithelial neoplasia often needs deeper excisions than for CIN.

2.12 The management protocols for colposcopy services in England are described in the NHSCSP's colposcopy and programme management guidelines (2016). Of the 188,179 people referred for colposcopy in England between 2015 and 2016, 61% had a treatment or procedure at their first appointment. The most common procedure was diagnostic biopsy (47%), followed by an excision (12%). The most common excision was a large-loop excision of the transformation zone (LLETZ; NHS Digital 2016).

2.13 Management is guided by a colposcopist's opinion of the extent of any abnormalities seen during colposcopy. If an abnormality is found, the colposcopist may take a diagnostic biopsy (punch biopsy). Or they may opt to treat an abnormality during the first clinic appointment ('see and treat') by excising the area of abnormal cells if they believe that high-grade changes are present. The NHSCSP's colposcopy and programme management guidelines (2016) recommend that treatment should not be offered at a person's first visit to a colposcopy clinic after referral for borderline or low-grade dyskaryosis. Ablative treatments should only be done after a diagnostic punch biopsy has been taken and the results have been checked.

2.14 Biopsies are examined by a histopathologist and the results are used to help the colposcopist decide whether treatment is needed. Typically, areas of CIN 2 or worse (known as CIN 2+) would need treatment. This can be done either by excising the area of abnormal cells or by destroying them in situ (ablation). During excision, cells are usually removed using a thin electrically-heated looped wire in the LLETZ procedure. The excised tissue is sent to histopathology to confirm the extent of the abnormality and to guide further management. LLETZ is usually done in the colposcopy clinic using local anaesthetic.

2.15 Unlike excisional treatment, cells removed by ablative treatment cannot be examined by a histopathologist because they are destroyed in situ. Ablative treatments include laser ablation, cryocautery and cold coagulation.

2.16 If cervical cancer is identified, depending on the stage, conservative treatment could be offered. Treatment options for cervical cancer include cone biopsy for very early stage disease, trachelectomy, hysterectomy, radiotherapy and chemotherapy.

3 The diagnostic tests

Two interventions and 1 comparator were included in this assessment.

The interventions

Dynamic Spectral Imaging System (DYSIS) colposcope with DYSISmap (DYSIS Medical)

3.1 The DYSIS colposcope is a CE-marked digital video colposcope. It uses spectral imaging technology and an inbuilt algorithm to produce an adjunctive map of the cervical epithelium, known as the DYSISmap (or pseudo-colour imaging). The DYSISmap is intended to be used with colposcopy to help detect cervical intraepithelial neoplasia (CIN).

3.2 The system comprises:

- a high-resolution digital colposcope, which incorporates an inbuilt display console and monitor for the clinician
- an optional additional monitor that allows the patient to see the images
- single-use or reusable specula
- an acetic acid applicator
- software
- a patient database (the patient management system) that stores images and videos from a colposcopy examination and records biopsy sites.

3.3 The device can be used as a standard digital video colposcope, but the spectral imaging technology used by the DYSIS colposcope also measures the speed, intensity and duration of aceto-whitening. These parameters are used to produce dynamic curves that plot intensity against time and an inbuilt algorithm assigns each area of the cervix a colour on the DYSISmap.

3.4 The DYSISmap is displayed on the screen, overlaid on a live image of the cervix, and can be used by the colposcopist to select areas for biopsy. The colour spectrum shown on the DYSISmap ranges from cyan, which represents weak aceto-whitening, to white, which represents intense aceto-whitening. The greater the intensity of the measured aceto-whitening reaction, the greater the likelihood of an abnormality. Imaging takes 3 minutes, but the colposcopist can stop it manually. However the company recommends that the system needs at least 125 seconds of imaging to allow it to calculate and display the DYSISmap.

ZedScan I

3.5 The ZedScan I is a CE-marked electrical impedance spectroscopy (EIS) system, which is designed to be used with colposcopy to help detect high-grade CIN. The system comprises:

- a portable handset, which takes EIS readings and displays the results to the user on an inbuilt interface
- a docking station
- single-use EIS sensors that are placed over the snout of the handset
- a software application, which incorporates a database to store results and can be installed onto a personal computer.

3.6 The device uses EIS to differentiate normal, precancerous and cancerous tissue by measuring the electrical properties of the cervical epithelial cells. Electrical impedance is measured at 14 different frequencies and a spectrum is produced, which varies according to the structure and properties of the tissue. The device can be used in scanning mode or in single-point mode. During scanning mode, and after acetic acid has been applied, the single-use EIS sensors take readings from between 10 and 12 sites on the cervical transformation zone. The readings are processed by the handset using an inbuilt algorithm, which quantifies the degree of abnormality (dysplasia) at each site and compares it with a reference value to give the user a semi-quantitative result. Results are displayed to the colposcopist on the inbuilt user interface. The results show the likelihood of high-grade CIN being present at each of the scanned sites.

3.7 The results provided by the device are intended to be used to guide a colposcopist to areas that need to be biopsied, when used with standard colposcopy. It is estimated that the device takes 2 to 3 minutes to scan the cervix and display the results. The results from the ZedScan I handset are automatically uploaded to the system's database through the docking station.

The comparator

Colposcopy

3.8 During colposcopy the cervix is assessed by a colposcopist using a colposcope, which is a low-powered microscope. The aim of colposcopy in the NHS cervical screening programme (NHSCSP) is to confirm whether a potential abnormality found by cervical screening is present, and if so, to assess the likely extent and grade of the abnormal cells. Binocular colposcopy is most often used in the NHS.

3.9 The NHSCSP's colposcopy and management guidelines (2016) state that when an adequate colposcopy has been done, that is when the transformation zone has been fully visualised, the colposcopic diagnosis should have a positive predictive value of 65% for a high-grade lesion (CIN 2 or worse [CIN 2+]).

4 Evidence

The diagnostics advisory committee (section 8) considered evidence on the DYSIS colposcope with DYSISmap (hereafter referred to as DYSIS) and the ZedScan I for detecting cervical intraepithelial neoplasia (CIN) from several sources. Full details are in the project documents for this guidance.

4.1 For the diagnostic accuracy review, studies were included if a prospective cohort had the index test or their prototypes (DYSIS or ZedScan I done in addition to colposcopy) and reference standard (histopathology) done independently, and contained enough data to allow diagnostic accuracy estimates to be calculated. For the effectiveness and implementation reviews, observational or experimental studies were included if DYSIS or ZedScan I, or their prototypes, were used in addition to colposcopy. All studies included in the diagnostic accuracy review were appraised using the QUADAS-2 tool. Studies in the implementation review were appraised using guidance from Burns et al. (2008) and the Centre for Evidence Based Management (2014).

4.2 In total, 12 studies were included: 11 in the diagnostic accuracy review, 3 in the review of clinical outcomes, and 5 in the implementation review. Some studies included outcomes that were relevant to more than 1 review. Most studies were reported in more than 1 paper or abstract.

Diagnostic accuracy

4.3 Of the 11 studies included in the diagnostic accuracy review, 9 included data for DYSIS and 2 included data for ZedScan (1 for ZedScan I and 1 for a prototype). All studies were done in hospital-based colposcopy clinics, and 6 were multicentre studies. Five studies included at least 1 centre in England (both ZedScan studies and 3 DYSIS studies). Most of the people in the studies were referred for colposcopy because of an abnormal screening result.

4.4 Of the 9 DYSIS studies, 1 was considered to be at low risk of bias and the other 8 at high risk of bias. Both ZedScan studies were considered to be at a high risk

of bias. The main source of bias in the studies was verification bias. This was because biopsies were not taken to confirm the absence of disease when the colposcopist did not identify any abnormalities because this is not generally considered to be good clinical practice. Concerns about the generalisability of the results of the ZedScan studies were highlighted because most of the people in the studies were examined at a single centre.

4.5 Meta-analyses were done for the diagnostic accuracy of DYSIS, which included 6 studies. Two studies were excluded because they only reported data for subgroups and 1 was included in a narrative analysis only. The analyses assume that 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 CIN 2 or worse (CIN 2+). No meta-analysis was done for the ZedScan studies.

DYSIS

4.6 The pooled results from the meta-analyses are summarised in table 1. The pooled positive predictive value of colposcopy was 55.78% (95% confidence interval [CI] 47.54% to 64.03%) and of DYSISmap with colposcopy was 43.60% (95% CI 33.12% to 54.07%). The corresponding negative predictive value of colposcopy was 86.70% (95% CI 80.17% to 93.22%) and of DYSISmap with colposcopy was 92.20% (95% CI 88.06% to 96.34%). A sensitivity analysis was done with a logistic regression model. Roensbo et al. (2015) was excluded because this study did not assess DYSIS with colposcopy directly but recorded whether a colposcopist agreed or disagreed with the DYSISmap. To examine the effect of verification bias, results were stratified by the number of biopsies taken in the studies when both DYSIS and colposcopy did not identify any areas of abnormality.

4.7 The results of the meta-analyses suggest that compared with colposcopy alone, DYSIS with colposcopy improves sensitivity for detecting CIN 2+, although this is associated with a reduction in specificity. However, the results of the logistic regression model show a statistically 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 (difference in log odds 0.04; p=0.84). This suggests that DYSIS increases the number of people suspected of having CIN 2+ and may therefore increase the number of biopsies taken. But it may not improve the ability to discriminate between lesions with and without CIN 2+ when compared with colposcopy. The results of the sensitivity analyses designed to explore verification bias in people with negative DYSIS and colposcopy examinations suggested that sensitivity and specificity estimates decline as the number of random biopsies taken increases.

4.8 An additional 5 studies were included in a separate narrative analysis. This confirmed the results of the meta-analyses; DYSIS improves sensitivity but reduces specificity when compared with colposcopy.

Table 1 Diagnostic accuracy of DYSIS

Analysis	Technology	Summary estimates: Sensitivity %	Summary estimates: Specificity %
Forest plots of diagnostic accuracy	Colposcopy (6 studies)[a]	58.40 (50.31 to 66.50)	86.46 (81.26 to 91.66)
Forest plots of diagnostic accuracy	DYSISmap alone (3 studies)[b]	59.18 (33.10 to 85.26)	81.64 (71.25 to 92.04)
Forest plots of diagnostic accuracy	DYSISmap plus colposcopy (6 studies)[a]	81.21 (77.35 to 85.07)	70.06 (60.31 to 79.82)
Hierarchical bivariate analysis	Colposcopy (6 studies)[a]	57.74 (49.7 to 63.4)	87.34 (79.7 to 92.4)
Hierarchical bivariate analysis	DYSISmap plus 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)

Analysis	Technology	Summary estimates: Sensitivity %	Summary estimates: Specificity %
Logistic regression model	DYSISmap plus colposcopy (6 studies)[a]	81.25 (72.2 to 87.9)	70.40 (59.4 to 79.5)
Sensitivity analyses: Logistic regression model (excluding Roensbo et al. 2015)	Colposcopy (5 studies)[c]	56.4 (47.5 to 64.9)	90.2 (86.3 to 93.1)
Sensitivity analyses: Logistic regression model (excluding Roensbo et al. 2015)	DYSISmap plus colposcopy (5 studies)[c]	82.9 (75.0 to 88.7)	72.9 (63.3 to 80.7)
Sensitivity analyses: 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)
Sensitivity analyses: Studies with no biopsies in negative examinations	DYSISmap plus colposcopy (3 studies)[d]	86.11 (79.6 to 92.7)	73.61 (50.0 to 97.2)
Sensitivity analyses: 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)
Sensitivity analyses: Studies with 1 random biopsy in negative examinations	DYSISmap plus colposcopy (Louwers et al. 2011, Soutter et al. 2009)	78.7 (72.6 to 85.6)	70.02 (57.9 to 82.2)
Sensitivity analyses: 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)
Sensitivity analyses: Studies with multiple random biopsies in negative examinations	DYSISmap plus 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; NPV, negative predictive value; PPV, positive predictive value.

References:

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).

ZedScan I

4.9 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 in table 2. Tidy et al. (in press) includes results for the current version of the device in a human papilloma virus (HPV) primary screening setting, but none for colposcopy alone. The results of the studies suggest that using ZedScan with colposcopy may have better sensitivity or specificity than colposcopy alone depending on the threshold used (which is set by the manufacturer). But when a regression model was fitted to the results from Tidy et al. (2013), the improvement in diagnostic accuracy was not quite statistically significant (difference in log diagnostic accuracy 0.488, p=0.078). However, only 1 study was available for analysis and the EAG commented that this is a conservative approach which should be considered as exploratory only.

Table 2 Diagnostic accuracy of ZedScan

Study	Colposcopy cut-off	Colposcopy alone: Sensitivity % (95% CI)	Colposcopy alone: Specificity % (95% CI)	ZedScan cut-off	ZedScan plus colposcopy: Sensitivity % (95% CI)	ZedScan plus colposcopy: Specificity % (95% CI)
Tidy et al. (in press) ZedScan I	–	Not reported	Not reported	Multiple	97.9 (96.6 to 99.2)	58.6 (55.1 to 62.1)

Study	Colposcopy cut-off	Colposcopy alone: Sensitivity % (95% CI)	Colposcopy alone: Specificity % (95% CI)	ZedScan cut-off	ZedScan plus colposcopy: Sensitivity % (95% CI)	ZedScan plus colposcopy: Specificity % (95% CI)
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)
Tidy et al. (2013) prototype device	Colposcopic impression	73.6 (64.3 to 82.8)	83.5 (76.5 to 90.5)	1.083	78.2 (69.5 to 86.8)	83.5 (76.5 to 90.5)
Tidy et al. (2013) prototype device	Colposcopic impression	73.6 (64.3 to 82.8)	83.5 (76.5 to 90.5)	1.568	62.1 (51.9 to 72.3)	95.4 (91.5 to 99.3)
Tidy et al. (2013) prototype device	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)
Tidy et al. (2013) prototype device	Disease present	88.5 (81.8 to 95.2)	38.5 (29.4 to 47.7)	0.390	96.6 (92.7 to 100)	38.5 (29.4 to 47.7)
Tidy et al. (2013) prototype device	Disease present	88.5 (81.8 to 95.2)	38.5 (29.4 to 47.7)	0.568	92.0 (86.2 to 97.7)	51.4 (42 to 60.8)

Note: 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.

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia.

4.10 Further data on ZedScan I were available in 2 substudies of Tidy et al. (in press).

In a conference abstract Tidy et al. (2016) reported that the performance of the technology varied across colposcopy clinics in England, Ireland and Germany, with sensitivity ranging from 73.1% to 100% and specificity from 25.7% to 58.1%. McDonald et al. (2017) evaluated the accuracy of ZedScan I in people with known high-risk HPV genotypes and compared its performance among 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 standard colposcopy was higher in the HPV 16 group (86.9%) than in the other high-risk genotypes group (79.7%).

4.11 A study including 91 people (Muszynski et al. 2017) was submitted during consultation. In 1 French hospital, using ZedScan I with colposcopy increased detection of people with high-grade lesions by 47.3%. The rate at which biopsies were taken also increased when making decisions using results from both ZedScan I and colposcopy, compared with using colposcopy alone. The reported sensitivity of ZedScan I with colposcopy was 93.3% compared with 61.3% for colposcopy alone. The reported specificity of ZedScan I with colposcopy was 34.4% compared with 80.0% for colposcopy alone.

Test positive rates

4.12 Test positive rates ranged from 21.22% to 55.51% for DYSIS 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 Soutter et al. 2009). In each study the test positive rate was always higher for DYSIS than for colposcopy alone.

4.13 Test positive rates ranged from 30.20% to 77.04% for ZedScan, depending on the cut-off used in the 2 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

4.14 Test failure rates (including failures not related to the technology) with DYSIS were reported in 6 studies and ranged from 2.9% to 31.4%. The highest failure rate was reported by Soutter et al. (2009), which included a prototype version of the system that had problems with unsatisfactory view and faulty acetic acid applicators. Failure rates for ZedScan (including failures not related to the technology) were reported in 2 studies. They were 5.6% (Zedscan I) and 13.6% (prototype; Tidy et al. in press and Tidy et al. 2013).

Biopsy rates

4.15 All diagnostic accuracy studies included in the external assessment group's (EAG) analysis included 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.

4.16 Two prepublication manuscripts by Cholkeri-Singh et al. (2018) and DeNardis et al. (2017), which included additional data from the IMPROVE-COLPO trial, were submitted during consultation. Diagnostic accuracy data from this study had been included in the EAG's analysis. IMPROVE-COLPO was an observational study done in 39 colposcopy clinics in the US.

4.17 Cholkeri-Singh et al. (2018) reported results of a 2-arm observational study in which people who were prospectively assessed using DYSIS were compared with historical controls (people assessed with standard colposcopy by the same colposcopists). The yield of CIN 2+ (defined as the proportion of people with at least 1 biopsy showing CIN 2+) was higher in the DYSIS group (9.48% compared with 7.21%; p=0.014). The yield of CIN 3+ was also higher in this group (3.23% compared with 2.07%; p=0.031). The number of people having biopsies between the groups was similar (71.6% compared with 71.5%), but the average number of biopsies per person was higher for the DYSIS group (1.26 compared with 1.03).

4.18 DeNardis et al. (2017) reported results of a cross-sectional observational study in which DYSISmap was used after an initial assessment with DYSIS video colposcopy to identify further sites for biopsy. DYSIS video colposcopy-directed

biopsies identified 78 people with CIN 2+; DYSISmap-assisted biopsies identified a further 34 people with CIN 2+. Also, DYSIS video colposcopy-directed biopsies identified 30 people with CIN 3+ and DYSISmap-assisted biopsies identified a further 15 people with CIN 3+. The positive predictive value of DYSIS video colposcopy-directed biopsies was 13.24% compared with 16.16% for DYSISmap-assisted biopsies.

Subgroup analyses

4.19 Data on referrals for low-grade and high-grade cytology suggested that colposcopy was less sensitive for detecting CIN 2+ in low-grade cytology referrals. No differences in sensitivity were seen for DYSIS and ZedScan I.

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

4.21 Founta et al. (unpublished) reported data from a test of cure population for whom the EAG calculated 95% confidence intervals. 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 was substantially different in this study compared with the summary estimates provided in the meta-analyses for all colposcopy referrals.

Clinical effectiveness

4.22 Data on adverse events were reported in 5 studies. In a ZedScan prototype study, 1 person felt unwell after the examination and 2 people had issues with bleeding after biopsies were taken. It is uncertain whether these events were related to using the ZedScan. No adverse events were reported in 4 DYSIS studies.

4.23 No data were found for morbidity and mortality associated with treatment and biopsy during colposcopy, or for health-related quality of life. There were insufficient data to determine whether the increased detection of CIN 2+ was

associated with a reduction in cervical cancer.

4.24 Two systematic reviews of adverse outcomes of CIN treatment were found. Kyrgiou et al. (2015) focused on fertility and early pregnancy outcomes (less than 24 weeks' gestation). People who had treatment 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) focused on obstetric (more than 24 weeks' gestation) and neonatal outcomes. People who had 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). The risk increased as the depth of the excision increased.

Implementation

4.25 Five studies were included in the implementation review. Of these, 3 were done 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

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

4.27 Louwers et al. (2015) gave a patient satisfaction questionnaire to 239 people who had a DYSIS examination. Results showed that 93.9% of people 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.

4.28 Budithi et al. (2017) gave questionnaires to both patients and colposcopists in 5 colposcopy clinics in Wales; 68 patients responded and 45 colposcopist responses were received (the number of colposcopists was not reported in the abstract). 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 responses received from colposcopists, 96% agreed or strongly agreed that they were confident about colposcopy and their decision-making in selecting biopsy sites. But only 48% went on to agree that DYSISmap affected their selection of 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.

Colposcopist experience

4.29 Coronado et al. (2014) surveyed 63 colposcopists with different levels of experience. A retrospective review of 50 colposcopy and DYSISmap images was also done. The study found that the correct diagnosis (either normal, low-grade lesion, high-grade lesion or cancer) was made more frequently with DYSIS than with standard colposcopy for colposcopists with low and medium levels of experience. There was no difference for highly experienced colposcopists. All groups agreed that DYSIS is better at directing diagnosis and provides more information than standard colposcopy. The survey also reported that using DYSISmap improved detection of CIN 2+ by colposcopists of all experience levels. However, the EAG noted that this was based on a small subgroup analysis of the retrospective review of stored images.

Cost effectiveness

Review of economic evidence

4.30 Two relevant economic evaluations were identified; 1 for DYSIS compared with colposcopy over a lifetime time horizon (Wade et al. 2013) and another for a

ZedScan prototype compared with colposcopy over a 3-year time horizon (Whyte et al. 2013). Wade et al. was produced for NICE's diagnostics guidance 4 on adjunctive colposcopy technologies and found that DYSIS dominated colposcopy (that is, DYSIS cost less and was more effective than colposcopy). Whyte et al. reported lower costs associated with the use of a prototype ZedScan device per person with CIN 2 or 3 treated, because it reduced both rates of overtreatment and the number of follow-up appointments needed for people with CIN 1. However, this was associated with a reduction in the number of CIN 2 or 3 lesions treated and a consequent reduction in the number of cancers detected. Neither study fully addressed the decision problem.

Modelling approach

4.31 The EAG developed a de novo economic model designed to assess the cost effectiveness of DYSIS and ZedScan I, used with colposcopy, in both an HPV triage and an HPV primary screening setting. The analyses took the perspective of the NHS and personal social services and had a 60-year (lifetime) time horizon. All costs and effects were discounted at 3.5%.

Model structure

4.32 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 identical patients. The model incorporated both screening and treatment pathways: 1 submodel simulated the natural history of CIN and cervical cancer, and another submodel simulated adverse obstetric outcomes for people who had treatment for CIN. The adverse obstetric outcome model captured 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 among infants born preterm. The natural history model was adapted from Kulasingam et al. (2013) with invasive cancer parameters taken from Campos et al. (2014).

4.33 At the beginning of the first cycle each person is referred for colposcopy and has

treatment if needed, before entering the natural history model. In subsequent cycles, the person can follow 1 of 4 screening and treatment pathways: no screening, colposcopy referral, routine screening, or a follow-up pathway for those who have had previous treatment, unless they died in the previous cycle. Every pathway ends with the person entering the natural history model.

4.34 The model was implemented using a random walk and for each person it simulated the following uncertain events occurring: disease progression, diagnostic results or treatment outcomes. The characteristics that determined the associated events and transitions for each person in the model were:

- age
- health state (clear, HPV, CIN 1, CIN 2 or 3, cancer)
- reason for referral for colposcopy (high-grade or low-grade cytology)
- next scheduled screening (routine call, 6-month cytology, 6-month colposcopy, test of cure, CIN 1 follow-up)
- time elapsed since last screening
- type of clinic visited ('see and treat' or 'watchful waiting').

Identical patients were run through each treatment strategy and random numbers were maintained across all runs of the model.

4.35 Two base cases were modelled: HPV triage and HPV primary screening. The modelled pathways for HPV triage were based on those outlined in the NHSCSP's colposcopy and programme management guidelines (2016). For HPV primary screening the modelled pathways were based on the testing algorithms used in the NHSCSP's pilot sites.

Model inputs: diagnostic accuracy estimates

4.36 The diagnostic accuracy estimates used in the model are shown in table 3.

Table 3 Accuracy estimates used in the model

Technology	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])	97.85 (96.5 to 99.2)	58.63 (55.1 to 62.1)

Abbreviation: CI, confidence interval.

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

Model inputs: underlying health states and reasons for referral

4.38 In the model, people referred for colposcopy have 2 initial characteristics; a true underlying health state (clear, HPV, CIN 1, CIN 2 or 3, or cancer) and a reason for referral (low-grade or high-grade lesions). These joint distributions were taken from the NHSCSP statistical bulletin (2015/16) for HPV triage and unpublished data provided by the NHSCSP pilot sites for HPV primary screening, and were influenced by disease prevalence and the accuracy of screening.

Model inputs: treatment probabilities

4.39 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 CIN 1 to 10.3% for

CIN 3. The probability of adverse obstetric outcomes after treatment was estimated by applying the relative risk of preterm birth (1.56) from Kyrgiou et al. (2016) to the probability of preterm birth for people with untreated lesions as reported in NICE's guideline on preterm labour and birth (7.3%). This gave an excess risk of 4.09% for preterm birth after LLETZ treatment.

Model inputs: costs

4.40 The average cost per person of using the technologies was calculated using information from companies and clinical experts. The costs include the capital cost of the technologies (spread over 15 years for a colposcope and over 5 years for DYSIS and ZedScan I), annual maintenance costs and consumable costs. To calculate the average cost per procedure, and to be consistent with Wade et al. (2013), it was assumed that 1,229 people per year were seen. The following costs per person were assumed:

- colposcopy: £3.75
- DYSIS: £9.24
- ZedScan I: £30.52.

4.41 Biopsy and treatment costs were taken from NHS reference costs. The cost of a cytology and HPV test were taken from the TOMBOLA study and inflated to 2016 prices. The values used in the model for screening events are shown in table 4.

Table 4 Costs of screening events

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

Abbreviations: HPV, human papilloma virus; LLETZ, large-loop excision of the transformation zone.

4.42 Cancer treatment costs were taken from Martin-Hirsch et al. (2007). Costs associated with adverse obstetric outcomes were taken from Lomas et al. (2016) and inflated to 2016 prices. It was assumed that a preterm birth costs £24,610, which takes into account initial inpatient neonatal care and ongoing costs for the first 18 years of life.

Model inputs: health-related quality of life and QALY decrements

4.43 Health-related quality-of-life estimates were taken from the published literature. The disutilities associated with screening, diagnosing and treating CIN were taken from Simonella and Canfell (2014) and are shown in table 5. Age- and gender-specific utilities from Kind et al. (1999) were applied to the HPV, CIN 1 and CIN 2 or 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 preterm birth (Lomas et al. 2016).

Table 5 Disutilities for screening, diagnosis and treatment of CIN

Screening event	QALY decrement
Negative cytology or HPV	0.0062
False positive referral for colposcopy	0.0276
Diagnosed CIN 1	0.0276
Treatment of CIN	0.0296

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; QALY, quality-adjusted life year.

Base-case results

4.44 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 CIN 2+.
- The probability of a positive colposcopy result was:
  - identical for people with clear, HPV or CIN 1 results
  - identical for people with CIN 2 or 3 or invasive cancer.
- The choice between a 'see and treat' clinic and a 'watchful waiting' clinic was independent of diagnostic accuracy.
- Biopsy and histopathology (the reference standard) were 100% accurate.
- Excision at the first colposcopy appointment was only possible for referrals for high-grade lesions with a positive colposcopy result.
- For low-grade lesion referrals, CIN 2+ was confirmed by diagnostic biopsy before treatment.
- CIN 1 lesions were not treated and people had a 12-month follow-up screening in the community.
- People whose lesions were treated for CIN remained at risk of preterm birth (before 37 weeks' gestation) for each year after treatment up to the age of 45.
- When cancer was detected, treatment was offered appropriate to the stage. An excess risk of mortality was applied for 5 years and decreased according to time since diagnosis.
- DYSIS or ZedScan I examinations were the same length as a standard colposcopy examination.
- ZedScan I was used for diagnostic colposcopies only.

4.45 There were 2 base cases: 1 for HPV triage and 1 for HPV primary screening. In a 'see and treat' clinic, treatment was done at the first visit for people who had a referral for a high-grade lesion according to cytology and a colposcopy examination graded as CIN 2+. In a 'watchful waiting' clinic, treatment was done at the second visit when the results of any diagnostic biopsies showed CIN 2+.

4.46 The results of the HPV triage base case showed that both technologies dominated standard colposcopy in 'see and treat' clinics (that is, they cost less and are more effective). In 'watchful waiting' clinics, DYSIS dominated standard colposcopy for low-grade lesion referrals and for all referrals combined, but had an incremental cost-effectiveness ratio (ICER) of £675 per QALY gained for high-grade lesion referrals compared with standard colposcopy. ZedScan I had an ICER of £272 per QALY gained for low-grade lesion referrals and £4,070 per QALY gained for high-grade lesion referrals. For all referrals, it had an ICER of £418 per QALY gained. Indirect comparisons suggest that ZedScan I always costs more but is more effective than DYSIS in both 'see and treat' and 'watchful waiting' clinics. The results of the HPV primary screening base case were similar to the HPV triage base case. The EAG highlighted that because the diagnostic accuracy of DYSIS and ZedScan I have not been compared directly, these results should be considered exploratory.

4.47 The number of treatments, biopsies and missed disease in each base case is shown in table 6. This table shows the cumulative occurrence of events over the lifetime of the modelled cohort, therefore an event can occur more than once per person. 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 in 'watchful waiting' clinics).

Table 6 Secondary outcomes per 1,000 people referred for colposcopy (60-year time horizon)

Clinic	Strategy	Missed CIN 2+*	Cancers	LLETZ	UnnecessaryLLETZ	Unnecessary diagnostic biopsy
HPV triage: 'See and treat'	Colposcopy	69	43	466	27	139
HPV triage: 'See and treat'	DYSIS	30	34	501	61	229
HPV triage: 'See and treat'	ZedScan I	3	29	524	82	291
HPV triage: 'Watchful waiting'	Colposcopy	69	44	449	0	137

Clinic	Strategy	Missed CIN 2+*	Cancers	LLETZ	UnnecessaryLLETZ	Unnecessary diagnostic biopsy
HPV triage: 'Watchful waiting'	DYSIS	30	37	465	0	260
HPV triage: 'Watchful waiting'	ZedScan I	3	32	477	0	347
HPV primary screening: 'See and treat'	Colposcopy	82	33	446	22	164
HPV primary screening: 'See and treat'	DYSIS	34	25	478	50	296
HPV primary screening: 'See and treat'	ZedScan I	4	20	498	68	386
HPV primary screening: 'Watchful waiting'	Colposcopy	82	34	432	0	172
HPV primary screening: 'Watchful waiting'	DYSIS	34	27	450	0	316
HPV primary screening: 'Watchful waiting'	ZedScan I	4	22	460	0	417

Note: * Missed CIN 2+ refers to the number of CIN 2+ cases not detected by the technologies (colposcopy, DYSIS, ZedScan I) rather than cases not detected following referral for colposcopy. In the model people with high-grade cytology referrals have a diagnostic biopsy and are identified as CIN 2+ even if a colposcopic examination is incorrectly negative.

Abbreviations: CIN 2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papilloma virus; LLETZ, large-loop excision of the transformation zone.

Scenario analyses

4.48 The following scenario analyses were done to explore the effect 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.

4.49 When the time horizon was restricted to 3 years, colposcopy dominated (that is, it cost less and was more effective) both DYSIS and ZedScan I in most scenarios except for high-grade lesion referrals in HPV triage '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. For 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, and because 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.

Sensitivity analyses

4.50 The following inputs were changed in sensitivity analyses to explore the effect of parameter uncertainty:

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

4.51 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, whereas the QALYs decreased. Under these assumptions ZedScan I 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 lesion referrals in HPV primary screening 'watchful waiting' clinics.

4.52 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 people per year were seen, it no longer dominated colposcopy in HPV primary screening 'watchful waiting' clinics and had an ICER of £270 per QALY gained for all referrals. None of the other sensitivity analyses changed the results substantially.

4.53 The ZedScan I results were sensitive to changes in the cost of diagnostic and treatment biopsies because of its increased sensitivity and lower specificity than colposcopy. When the cost of a diagnostic biopsy was increased to £102.72 and a treatment biopsy (LLETZ) to £490.89, ZedScan I no longer dominated colposcopy for low-grade lesion referrals and all referrals combined. Under these assumptions, its highest ICER was £6,709 for high-grade referrals to an HPV primary screening 'watchful waiting' clinic. None of the other sensitivity analyses changed the results substantially.

5 Committee discussion

Current practice

5.1 The committee discussed current practice for assessing suspected cervical abnormalities in a colposcopy clinic. The clinical experts explained that NHS clinics most often use binocular colposcopy, which allows a colposcopist to examine a cervix and take both diagnostic and treatment biopsies under direct visualisation. Acetic acid is used to highlight areas of abnormality. The committee noted that colposcopy is associated with both intra- and inter-observer variability because it is a visual examination that is highly dependent on the colposcopist's expertise. The committee considered the role of the adjunctive colposcopy technologies and was advised by the clinical experts that the technologies could provide less subjective results and help colposcopists select areas for biopsy. The clinical experts also explained that the technologies could help identify high-grade lesions in people referred for colposcopy because of low-grade cytology.

5.2 The committee noted that a series of changes are being made to the screening pathways used in the NHS cervical screening programme (NHSCSP). Human papilloma virus (HPV) triage was fully implemented in England in April 2014. HPV primary screening is currently being done in several pilot sites, with full implementation in England expected in 2019. These changes could affect referrals to colposcopy clinics and consequently the prevalence of high-grade disease, particularly when people with a HPV-positive cytology-negative screening result are seen in colposcopy. The committee concluded that there had been substantial changes to the care pathways since NICE's first diagnostics assessment of the DYSIS colposcope with DYSISmap in 2012.

Diagnostic accuracy and clinical effectiveness

5.3 The committee discussed the external assessment group's (EAG) critical appraisal of the included diagnostic accuracy studies. It noted that the greatest risk of bias in the studies occurred because not all patients had the reference

standard test (colposcopically directed biopsies and histopathology). In most studies, people who had a negative colposcopy did not have biopsies taken. The clinical experts explained that it was not considered good clinical practice to take biopsies when there was no clinical indication. But the committee noted that the EAG's sensitivity analyses on the effect of verification bias showed that the more random biopsies taken, the lower the estimates of both sensitivity and specificity. The committee concluded that the diagnostic accuracy estimates provided by the included studies were likely to have been influenced by verification bias, and highlighted that future studies should aim to minimise this when possible.

5.4 The committee considered the applicability of the diagnostic accuracy studies that were done outside the UK. The clinical experts explained that the quality assurance measures for colposcopy done outside the UK are different to those in the UK, and that this was likely to influence the accuracy of colposcopy. The committee noted that the NHSCSP recommends that a satisfactory colposcopy should have a 65% positive predictive value for CIN 2+. It considered that although positive predictive value was likely to be influenced by several confounding factors, video colposcopy in the DYSIS studies did not achieve this benchmark, with a pooled positive predictive value of 55.78%. However, the committee noted that because this value depends on disease prevalence, the use of positive predictive value to assess the generalisability of studies to UK practice is problematic. The clinical experts also noted that the pooled sensitivity of colposcopy in the DYSIS studies was lower than they would expect to see in the UK. They also noted that in the ZedScan I study, which was done in the UK and used binocular colposcopy, a higher sensitivity for colposcopy was reported. The committee concluded that because of differences in colposcopy practice, such as fewer quality assurance measures and the use of video colposcopy, the accuracy data from non-UK studies may not be generalisable to the NHSCSP.

5.5 The committee considered the potential for the adjunctive colposcopy technologies to reduce both intra- and inter-observer variability. The companies explained that the technologies are designed to reduce the subjectivity of colposcopy by providing more objective results, but noted that no data on the reproducibility of the tests had been presented for the assessment. However, the committee noted published data suggesting that clinicians felt that the DYSISmap improved their confidence when selecting biopsy sites. It concluded that the technologies had the potential to help standardise colposcopy examinations, but

that insufficient data were available to determine whether this benefit would be realised in NHS clinical practice.

5.6 The committee discussed the results of the diagnostic accuracy analyses for the DYSIS colposcope with DYSISmap and the ZedScan I. It noted that although the accuracy estimates for colposcopy alone in the DYSIS and ZedScan studies varied considerably, the estimates suggested that the technologies were more sensitive but less specific than colposcopy alone. It considered that in practice this would result in a reduced false negative rate with more people being diagnosed with CIN 2 or worse (CIN 2+). But this could be at the expense of a higher false positive rate with more people having unnecessary diagnostic biopsies and treatment. The committee further noted that the diagnostic odds ratios, which had been calculated by the EAG for the DYSIS colposcope with DYSISmap studies, suggested that there was no difference between the accuracy of DYSIS colposcopy alone and DYSIS colposcopy with DYSISmap. The committee concluded that the results of the diagnostic accuracy studies suggest that it is plausible that the adjunctive colposcopy technologies may change the test threshold so that more people have biopsies, but without improving colposcopists' ability to differentiate between high- and low-grade disease.

5.7 The committee discussed the Cholkeri-Singh et al. (2018) and DeNardis et al. (2017) studies, submitted as prepublication manuscripts during consultation. These provided data from the IMPROVE-COLPO study. It acknowledged that these studies provide real world outcome data on the number of biopsies taken and supplement the diagnostic accuracy data in the EAG's systematic review. The committee noted that the results of the Cholkeri-Singh et al. study show that DYSIS with DYSISmap detects additional cases of both CIN 2 and CIN 3, relative to standard colposcopy, without increasing the number of people having biopsies. The committee considered the design of this study and noted a lack of detail on the methods used to ensure that controls in the retrospective arm were comparable with the people in the prospective arm. However, the committee heard from the EAG that the people in the 2 study arms appear to be comparable for key baseline characteristics. The committee also considered analyses provided at consultation based on KC65 data (from the NHSCSP in England between 2012/13 and 2015/16). It noted that the data generally showed no increase in biopsy rates in centres adopting DYSIS, but it acknowledged that DYSIS may not be used for every colposcopy in these centres. The committee

concluded that despite these papers having methodological limitations, combined with the KC65 data they provided some reassurance that the increase in biopsies implied by the results of the diagnostic accuracy studies alone may not be realised in practice in centres using DYSIS colposcopy with DYSISmap.

5.8 A patient expert explained that referral for colposcopy can often cause substantial anxiety, which may not reduce even when the colposcopy is normal. People having a colposcopy may be anxious because of the examination itself and because they have already had a screening result informing them that an abnormality has been detected. The clinical experts explained that it can often be difficult to reduce anxiety in people who have a negative colposcopy, but who were referred with an HPV-positive result, because no treatment can be offered. The committee noted evidence from the systematic review and also anecdotal evidence from clinical and patient experts, which suggested that the adjunctive colposcopy technologies could reduce anxiety because people can be shown objective information to explain that no abnormality has been detected. The committee concluded that although the additional information provided by the adjunctive colposcopy technologies has the potential to help clinicians reassure people and reduce their anxiety, there are currently insufficient data to conclude that they have a significant effect on this (see section 6.3).

Cost effectiveness

5.9 The committee discussed the assumption made in the cost-effectiveness model that video colposcopy and binocular colposcopy are equivalent in terms of diagnostic accuracy. The clinical experts explained that there was no consensus among experts about their equivalence and that the sensitivity estimates for video colposcopy obtained in the DYSIS studies were lower than would be expected for binocular colposcopy in the NHS. Also, the clinical experts noted that the estimates for the sensitivity of binocular colposcopy in the ZedScan studies were higher, and more representative of NHS practice. But the committee noted that the estimates used in the cost-effectiveness model for colposcopy alone were taken from the meta-analyses of DYSIS colposcopy. Therefore, the committee concluded that the relative benefits of the adjunctive colposcopy technologies could have been overestimated in the modelling.

5.10 The committee discussed both modelled base cases and noted that the increased sensitivity of the adjunctive colposcopy technologies led to less cervical cancers developing over the 60-year time horizon. The clinical experts explained that the additional high-grade lesions detected using the adjunctive colposcopy technologies could in fact be low-volume CIN 2 disease, which could regress without treatment. The committee questioned whether data were available that explained the natural history of low-volume CIN 2 but heard that these were not available. Anecdotal evidence, and results of a British Society for Colposcopy and Cervical Pathology survey, suggest that some clinicians are now using either ablative techniques or 'watchful waiting' management strategies for low-volume CIN 2 in some circumstances. The committee also noted that when the time horizon of the model was reduced to 3 years, and the longer-term outcomes associated with increased sensitivity were removed, colposcopy alone dominated; that is, it was more effective and less expensive than the adjunctive colposcopy technologies. The committee concluded that, without clinical outcome data, or data on the natural history of low-volume CIN 2, there was uncertainty about the longer-term outcomes associated with the increased sensitivity of the adjunctive colposcopy technologies. It wished to encourage further data collection to resolve this (see section 6.4).

5.11 The committee discussed the effect of the lower specificity associated with the adjunctive colposcopy technologies on longer-term outcomes in the model. In the shorter term, the model showed that reduced specificity is associated with an increase in unnecessary biopsies and treatments. The committee questioned whether this would be realised in practice. The EAG advised that the assumptions made in the model about when biopsies would be taken were based on the NHSCSP's colposcopy and programme management guidelines (2016; publication number 20). The clinical experts explained that these guidelines may not always be followed, and colposcopists may take biopsies for reassurance that high-grade disease is not present. The committee noted that there is considerable variation in clinical practice between colposcopists, and that there were no data to show how the adjunctive colposcopy technologies affect clinical decision-making in the UK. The committee also noted its previous conclusion (see section 5.7) that results from the prepublication version of Cholkeri-Singh et al. (2018) study and the KC65 data (from the NHSCSP in England between 2012/13 and 2015/16) showed no increase in biopsy rates in centres adopting DYSIS. It also noted that Cholkeri-Singh et al. reported that using DYSIS was associated

with an increased yield of CIN 2+ which, combined with the data on biopsy rates, suggests that DYSIS helps colposcopists target the areas chosen for biopsy. The committee concluded that there is some real world evidence suggesting that DYSIS does not increase the biopsy rate to the extent predicted by the model, and noted that equivalent data were not yet available for ZedScan I.

5.12 The committee discussed whether reduced specificity is associated with an increased risk of adverse obstetric outcomes in the longer term. The clinical experts explained that the relationship between biopsies, treatment and adverse obstetric outcomes was not well understood, but it was generally acknowledged that the smaller the excisional treatment the lower the risk of adverse outcomes. The committee noted that the base case assumed an excess risk of preterm delivery of 0.04, which was reduced to 0 in a scenario analysis with no substantial effect on the results. The committee concluded that although they were an important clinical consideration in practice, the longer-term effects of reduced specificity did not seem to be a key driver in the model.

5.13 The committee questioned the cost savings of the adjunctive colposcopy technologies in the model. The EAG explained that the model's cost savings were driven by increased sensitivity, which led to a reduction in costs associated with both cancer treatment and follow-up appointments. The clinical experts noted that technologies that improve the negative predictive value of colposcopy may become more important after HPV primary screening is fully rolled out and people with HPV-positive, cytology-negative results are referred for colposcopy. The committee noted that the base case for HPV primary screening was based on preliminary data only, but acknowledged that improvements in sensitivity may become increasingly important in the future. The committee concluded that because there were no data on the natural history of low-volume disease, it was uncertain whether the adjunctive colposcopy technologies would increase the detection of disease that would progress to cancer if not treated. Therefore, the cost savings in the model may not be robust.

5.14 The committee questioned the effect of not having a probabilistic sensitivity analysis to quantify the overall uncertainty in the model. The EAG explained that it could not do this analysis because of the length of time needed to run each simulation. The EAG also explained that although the mean ICER may be different from the deterministic analyses if the model was run probabilistically, there was

unlikely to be a substantial difference that would change the modelling conclusions. The committee noted that the model results had been robust to changes in many parameter estimates and assumptions in the deterministic sensitivity and scenario analyses, but that the results were likely to be confounded by the lack of clinical outcome data. The committee concluded that on this occasion the lack of a probabilistic sensitivity analysis was not critical.

5.15 The committee considered whether the adjunctive colposcopy technologies should be recommended for routine adoption. It noted its conclusions on the applicability of data from non-UK studies where the accuracy of colposcopy may differ (see section 5.4), the lack of data on the natural history of low-volume CIN 2 (see section 5.10) and the uncertainty about whether the adjunctive colposcopy technologies would reduce cervical cancer over the longer term (see section 5.13). Taking these factors into account, the committee considered that there was uncertainty about the clinical and cost effectiveness of the adjunctive colposcopy technologies because only diagnostic accuracy data were available. It noted, however, that further data (prepublication versions of Cholkeri-Singh et al. 2018 and DeNardis et al. 2017) provided at consultation showed that DYSIS was able to detect more CIN 3 lesions than standard colposcopy, without increasing the number of people having biopsies. Therefore, the committee concluded that there was enough evidence that colposcopy using DYSIS with DYSISmap detects more clinically important lesions than colposcopy alone to recommend its continued adoption. It also noted that the additional data provided at consultation were from a US study. The committee wished to encourage centres using DYSIS to audit their outcomes and confirm that the expected benefits are achieved in the NHS (see section 5.16). Also, the committee concluded that although the ZedScan I shows promise, there was too much uncertainty over clinical and cost effectiveness to recommend its routine adoption at present, and recommended that further research was needed (see section 5.17).

Research considerations

5.16 The committee recalled that the available clinical outcome data that support using DYSIS with DYSISmap were from a US study (see section 5.15). It therefore recommended that centres using this technology should audit their clinical

outcomes and confirm that the expected benefits are achieved in the NHS. Outcomes that should be audited include, but are not limited to, rates of CIN 2+ detection, CIN 3+ detection and biopsy.

5.17 The committee considered the amount of evidence available for both adjunctive technologies. It noted that more data were available for the DYSIS system, and that evidence for ZedScan I was limited to a small number of diagnostic accuracy studies. The committee considered that ZedScan I shows promise but further studies are needed, in particular to compare the accuracy and the clinical effectiveness of the technology with standard colposcopy.

5.18 The clinical experts explained that all colposcopy clinics complete a quarterly data return for Public Health England, the KC65. This is used to compare and assess their data against the standards outlined in NHSCSP's colposcopy and programme management guidelines (2016). The committee considered whether these data could be studied to see if biopsy and detection rates of CIN 2+ had increased in centres that had already adopted DYSIS colposcopy with DYSISmap or the ZedScan I. The clinical experts explained that the device used in each colposcopy is not currently recorded and it is not known whether centres with an adjunctive colposcopy technology use it routinely. The committee acknowledged that making the necessary changes to the KC65 to collect these data would be difficult. However, it wished to encourage the owners of the KC65 dataset to consider whether it could be adapted in the future and used to support further data collection for the adjunctive colposcopy technologies, and whether papers based on the data could be published and used for updates of this guidance. The committee also suggested that, if it is not possible to use the KC65 to collect these data nationally, then local audits should be used to collect these data from services that have adopted the adjunctive technologies.

5.19 The committee identified that different thresholds had been used to assess the accuracy of colposcopy in the studies. Some used colposcopic impression that high-grade disease was present (that is, what the colposcopist thought). In other studies colposcopy was considered positive if at least 1 measurement point was suggested for biopsy (that is, what action was taken). Some studies used both. This made comparison of the relative cost effectiveness of the adjunctive technologies difficult. The committee considered that a more consistent approach to assessing and reporting colposcopic accuracy in studies would help

future comparisons of adjunctive technologies. The clinical experts stated that work on producing standards for reporting colposcopic accuracy in the NHSCSP is being done.

5.20 The committee noted the assumption made in the cost-effectiveness model that video colposcopy and binocular colposcopy are equivalent in terms of diagnostic accuracy (see section 5.9). The clinical experts explained that there is limited evidence to support this assumption. Future assessments of adjunctive technologies would benefit from research assessing the equivalence of different types of colposcope (digital, video and binocular).

6 What research is needed

6.1 The committee noted that human papilloma virus (HPV) primary screening is being implemented across England (see section 5.2) and that the base-case economic modelling for HPV primary screening in this assessment was based on preliminary data only (see section 5.13). The committee recommended that further studies should be done in a HPV primary screening setting. These studies should incorporate clinical outcome data and be designed to minimise verification bias. Future studies should consider measuring variability and should also take into account HPV genotyping status when possible, so that the difference in accuracy in a population vaccinated against HPV types 16 and 18 can be better understood.

6.2 The committee noted that there were no data to show how the adjunctive colposcopy technologies affect UK clinical decision-making, when all colposcopy is done by accredited colposcopists (see section 5.11). It therefore recommended that data should be collected to show how the results of the technologies affect decision-making, including biopsy decisions and decisions to discharge people with a negative colposcopy examination back to routine screening.

6.3 The committee considered that the adjunctive colposcopy technologies had the potential to improve patient experience and reduce anxiety (see section 5.8). Further research is needed to understand the effect of having the additional information provided by the adjunctive colposcopy technologies on anxiety for people having a colposcopy, when this information is shown to a person during the examination.

6.4 The committee recommended that further research is needed to better understand the natural history of low-volume cervical intraepithelial neoplasia (CIN) 2 lesions. It noted that this is not captured in the current versions of the natural history models for CIN and cervical cancer (see section 5.10), but is likely to become increasingly important for colposcopy services as HPV primary screening is rolled out and vaccinated groups enter the screening programme.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database and highlight these recommendations to public research bodies.

8 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland
Chair, Diagnostics Advisory Committee (to October 2017)

Dr Mark Kroese
Chair, Diagnostics Advisory Committee, (from September 2017, previously Vice Chair)

Mr John Bagshaw
In-vitro Diagnostics Consultant

Professor Enitan Carrol
Chair in Paediatric Infection, University of Liverpool

Dr Sue Crawford
GP Principal, Chillington Health Centre (to August 2017)

Dr Owen Driskell
Lead for Laboratory Medicine, National Institute for Health Research Clinical Research Network West Midlands

Dr Steve Edwards
Head of Health Technology Assessment, BMJ Evidence Centre

Dr Simon Fleming
Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray
Consultant Microbiologist, Birmingham Children's Hospital

Dr Shelley Rahman Haley
Consultant Cardiologist, Royal Brompton and Harefield NHS Foundation Trust (from September 2017)

Professor Steve Halligan
Professor of Radiology, University College London

Mr John Hitchman
Lay member

Professor Chris Hyde
Vice Chair, Diagnostics Advisory Committee and Professor of Public Health and Clinical Epidemiology, Exeter Test Group, University of Exeter

Mr Patrick McGinley
Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

Dr Michael Messenger
Deputy Director and Scientific Manager NIHR Diagnostic Evidence Co-operative, Leeds

Mrs Alexandria Moseley
Lay member

Dr Peter Naylor
GP, Wirral

Dr Dermot Neely
Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Dr Simon Richards
Vice President Regulatory Affairs, Europe and Middle East, Alere Inc

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Professor Matt Stevenson
Professor of Health Technology Assessment, School of Health and Related Research, University of Sheffield

Professor Anthony Wierzbicki
Consultant in Metabolic Medicine/Chemical Pathology, St Thomas' Hospital

Specialist committee members

Miss Fran Berry
Lay member

Mr Christopher Brewer
Consultant Obstetrician and Gynaecologist, York Teaching Hospital NHS Foundation Trust

Dr Suha Deen
Consultant Gynaecological Pathologist, Nottingham University Hospitals NHS Trust

Mrs Phyllis Dunn
Clinical Lead Nurse, University Hospitals of North Midlands NHS Trust

Miss Theresa Freeman-Wang
Consultant Gynaecologist, Whittington Health NHS Trust

Dr Sadaf Ghaem-Maghami
Honorary Consultant Gynaecological Oncologist, Imperial College London

Professor Jane Macnaughton
Professor of Medical Humanities and Honorary Consultant in Obstetrics and Gynaecology, Durham University

Miss Hema Nosib
Consultant Gynaecologist, North West Anglia NHS Foundation Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Thomas Walker
Topic Lead (from September 2017)

Rebecca Albrow
Topic Lead (to August 2017) and Technical Adviser (from September 2017)

Frances Nixon
Technical Adviser (to August 2017)

Robert Fernley
Project Manager (to August 2017)

Donna Barnes
Project Manager (from September 2017)

Update information

Minor changes since publication

December 2025: Diagnostics guidance 32 has been migrated to HealthTech guidance 467. The recommendations and accompanying content remain unchanged.

ISBN: 978-1-4731-7374-3