NICE National Institute for Health and Care Excellence

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Diagnostics Assessment Programme

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

## Final scope

January 2017

## *1 Introduction*

In March 2016, following a review proposal and public consultation it was determined that NICE diagnostics guidance 4 on adjunctive colposcopy technologies for examination of the uterine cervix – DySIS and the Niris Imaging system should be updated. During the development of the review proposal it was identified that there had been changes in CE marking and that there are planned developments to the care pathway, therefore a standard update to the guidance is needed. The final scope was informed by discussions at the scoping workshop on 22 November 2016 and the assessment subgroup meeting on 7 December 2016.

A glossary of terms and list of abbreviations are provided in appendices A and B.

## *2 Description of the technologies*

This section describes the properties of the diagnostic technologies based on information provided to NICE from the companies and information available in the public domain. NICE has not carried out an independent evaluation of this description.

### 2.1 Purpose of the medical technologies

The adjunctive colposcopy technologies are intended to be used in conjunction with conventional colposcopy to aid the identification of 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. The adjunctive colposcopy technologies aim to provide an objective evaluation of cellular changes, known as CIN, using methods such as optical or electrical impedance spectroscopy to assess the characteristics of cervical

cells. CIN is a term that is used to describe precancerous changes in cells on the surface of the cervix (the cervical epithelium). Most cellular changes arise in an area of the cervix known as the transformation zone which is found where the endocervical canal (the internal canal of the cervix) meets the external part of the cervix. This is the area of the cervix that is sampled during a cervical screening test, and visualised and examined during a colposcopy examination.

The results provided by the technologies can help a colposcopist to determine whether further treatment or biopsies are needed, by guiding them to areas that are most likely to be abnormal. Where the results do not suggest any areas of abnormality, and the conventional colposcopy examination was normal, the colposcopist can be more confident that high grade disease is unlikely to be present. Use of the devices may result in more accurate detection of cervical abnormalities and consequently reduce the number of biopsies and follow-up colposcopy examinations that are required. In addition, the devices may also help a colposcopist select areas for biopsy more precisely and help to facilitate more conservative treatment for some people.

## 2.2 Product properties

### *2.2.1 DYSIS with DYSIS map (DYSIS Medical)*

The Dynamic Spectral Imaging System (DYSIS) colposcope is a CE marked high resolution digital video colposcope which uses spectral imaging technology and an inbuilt algorithm to produce an adjunctive map of the cervical epithelium which is known as the DYSIS map (or pseudo-colour imaging). The DYSIS map is intended to be used as an adjunct to colposcopy to aid the detection of cervical intraepithelial neoplasia (CIN).

The system comprises a high resolution digital colposcope which incorporates an inbuilt display console and monitor for the clinician, an optional patient monitor which enables the patient to view the images, single use or reusable speculums, an acetic acid applicator, software and a patient database (the patient management system) which can store images and videos from a colposcopy examination and can be used to record biopsy site locations. The system is HL7 and DICOM compatible to facilitate integration with hospital networks.

In the first instance the device can be used as a digital video colposcope. To use the spectral imaging functionality the imaging head has to be coupled with the speculum to prevent movement during imaging. The DYSIS map is produced during the period of the aceto-whitening reaction that occurs on the cervical epithelium (the surface of the cervix) when the colposcopist applies

acetic acid using the acetic acid applicator. A sensor detects the application of acetic acid and prompts the system to begin imaging. The spectral imaging technology used by the DYSIS colposcope measures the speed, intensity and duration of aceto-whitening. These parameters are used to produce dynamic curves which plot intensity against time and an inbuilt algorithm assigns each area of the cervix a colour on the DYSIS map which corresponds to the likelihood of an abnormality being present.

The DYSIS map 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 DYSIS map 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. The image of the cervix displayed on the screen can be magnified and have blue or green filters applied, and a high contrast mode is also available. These features are intended to aid the identification of abnormal blood vessels and other morphological features which can help a colposcopist grade the severity of an abnormality.

Imaging takes 3 minutes, but can be stopped by the colposcopist manually. However the company recommends that at least 125 seconds of imaging is needed to allow the system to calculate and display the DySIS map. The currently available version of DYSIS is DYSIS version 3, but the company intend that this will be superseded by the DYSIS touch and DYSIS ultra colposcopes in 2017. Each updated version of the system has had modifications to both the hardware and software, but the DYSIS map algorithm has remained unchanged.

### *2.2.2 ZedScan I (Zilico)*

The ZedScan I is a CE marked electrical impedance spectroscopy (EIS) system which is designed to be used as an adjunct to colposcopy to aid the detection of high grade CIN. The system is comprised of 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 which are placed over the snout of the handset, and a software application which incorporates a database to store results and can be installed onto a PC. The device is intended to be used alongside a conventional colposcope.

The device uses EIS to differentiate between normal, pre-cancerous and cancerous tissue by measuring the electrical properties of the cells on the surface of the cervix. These properties are known to differ between normal epithelial cells and those which are undergoing changes associated with various grades of neoplasia. 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 a scanning mode or in a single point mode. During scanning mode, the single use EIS sensors take readings from between 10 and 12 sites on the cervical transformation zone after the application of acetic acid. The readings are processed by the handset using an inbuilt algorithm which quantifies the degree of abnormality (dysplasia) at each reading site with a reference value providing a semi-quantitative result to the user. Results are displayed to the colposcopist on the in-built user interface. The results indicate the likelihood of high grade CIN being present at each of the sites scanned. The handset display uses coloured circles to indicate the location and results from each measurement point:

- Clear/white – no reading
- Green - high-grade CIN is unlikely to be present
- Amber – high-grade CIN is likely to be present
- Red – the highest likelihood that high-grade CIN is present

The device includes an automatic internal quality assessment before each reading is taken to check that the EIS sensor has sufficient contact with the cervix and the area of the cervix is suitable for readings. If the area has failed the quality assessment a reading will not be provided for that site. The results provided by the device are intended to be used to guide a colposcopist to areas which require biopsy when used in conjunction with standard colposcopy. It is estimated that the device takes 2 to 3 minutes to scan the cervix and display the results. The device can also be used in a single point mode to help select sites for diagnostic biopsy after the initial 10-12 readings have been taken. When operating in single point mode the results are displayed immediately and are shown on both the handset screen and via LEDs which are located on the snout of the handset so that the device can be held in position whilst the biopsy is taken. The results from the ZedScan I handset are automatically uploaded to the system's database via the docking station.

The company state that in cases where the referral cytology suggests a glandular abnormality, that is cervical glandular intraepithelial neoplasia (CGIN), the Zedscan I should only be used to detect co-existing high grade CIN as the accuracy of the ZedScan I for the detection of high grade CGIN has not been established at present.

# 3 Target conditions

## 3.1 Cervical intraepithelial neoplasia and cervical cancer

Cervical cancer is one of the less common cancers in the UK, largely because of the NHS Cervical Screening Programme. In 2013 there were 3,200 cases of cervical cancer (Cancer Research UK) in the 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 papillomavirus, hereafter referred to as high-risk HPV (hr-HPV), which causes changes in the cervical cells leading to abnormalities (pre-cancerous changes or cervical intraepithelial neoplasia [CIN]) which can progress into cervical cancer if not treated.

CIN can be classified using a grading scale which ranges from CIN1 (low grade) to CIN 3 (high grade). Grades 2 and 3 may often be referred to as high grade and are usually treated to prevent possible progression into cervical cancer, although expert advice suggests that CIN2 may be managed more conservatively in people who have smaller lesions and who have not completed their family. CIN is classified according to the depth of abnormal cells within the surface layer of the cervix observed on a diagnostic or excisional (treatment) biopsy:

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

Treatment for CIN aims to remove the cells either by excision or ablation. Of all non-diagnostic biopsies, that is excisional treatment biopsies, with a known result in 2014-15, 24% showed CIN 1 or less, 25.8% showed CIN 2, 46.1% showed CIN 3, 2.4% showed adenocarcinoma in situ, 1.6% showed cancer, and 0.2% were inadequate for assessment (Health and Social Care Information Centre, 2015). Less frequently, abnormalities occur on the inside of the cervical canal instead of the surface, and these changes are known as cervical glandular intraepithelial neoplasia (CGIN). Treatment for CGIN often requires deeper excisions than are required for CIN.

## 3.2 Patient issues and preferences

Referral for a colposcopy examination, and any associated treatment, often causes anxiety (O'Connor et al. 2016). People who are referred for

colposcopy are often concerned about the examination itself and having an abnormal cervical screening result, particularly as this could be associated with having cervical cancer. The colposcopy examination, diagnostic biopsies and treatment can often cause pain and discomfort. Although the adverse effects of biopsies and treatment are often short term, evidence suggests that treatment may be associated with adverse outcomes in subsequent pregnancies for some people (see section 6). Therefore people who have not completed their family may wish to opt for more conservative treatment.

If the adjunctive colposcopy technologies are able to reduce the number of colposcopy follow up appointments and biopsies needed, this may be more preferable to patients. Further, the additional information that is provided by the technologies may aid the colposcopist in providing an explanation of the results of the examination to the patient and provide increased reassurance, particularly where both the conventional colposcopy examination and the results given by the technologies indicate that no abnormalities are present.

## 3.3 Diagnostic and care pathway

### *3.3.1 Cervical screening*

Pre-cancerous changes to cells in the cervix are detected by cervical screening. The NHS Cervical Screening Programme invites people aged 25 to 64 to have a cervical screening test; people aged 25 to 49 are invited every 3 years, and people aged 50 to 64 every 5 years. Cervical screening involves a sample of cells being taken from the cervix using a specially designed brush. The cells are preserved using liquid based cytology kits which include vials containing a preservative fluid, and are sent to a cytology laboratory where they are examined under a microscope. In 2014-15, 3.04 million cervical cytology samples from GPs and NHS community clinics were processed. Of these samples, 2.5% did not contain sufficient cellular material to be reliably assessed and were classed as inadequate tests. Of all people with adequate tests, 93.6% had a negative test result and 6.4% had an abnormal result (Health and Social Care Information Centre, 2015).

The criteria used for reporting cervical cytology and corresponding management protocols for results are outlined in the NHS Cervical Screening Programme's third edition of Achievable standards, Benchmarks for reporting, and Criteria for evaluating cervical cytopathology [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. The detection of dyskaryotic cells suggests that CIN may be present. Grading systems for cervical cytology differ by country and the current system used in the NHS is shown in table 1. The table also includes a comparison to other grading

systems because data used in the assessment may be reported using these alternative systems.

**Table 1 Cervical cytology reporting terminology**

| **BSCC 1986 (previous NHS system)** | **ABC3 (current NHS system)** | **Bethesda system (used in the US)** |
|---|---|---|
| Inadequate | Inadequate | Unsatisfactory for evaluation |
| Negative | Negative | Negative for intraepithelial lesion or malignancy |
| Borderline change | Borderline change in squamous cells | ASC-US: Atypical squamous cells of undetermined significance (ASC-US) |
| | Borderline change in endocervical cells | |
| Mild dyskaryosis | Low-grade dyskaryosis | LSIL: Low grade squamous intraepithelial lesion |
| Borderline change with koilocytosis | | |
| Moderate dyskaryosis | High-grade dyskaryosis (moderate) | HSIL: high grade squamous intraepithelial lesion<br>ASC-H: cannot exclude high-grade squamous intraepithelial lesions (treat as HSIL) |
| Severe dyskaryosis | High-grade dyskaryosis (severe) | |
| Severe dyskaryosis ?invasive | High grade dyskaryosis /?invasive squamous carcinoma | Squamous cell carcinoma |
| ?glandular neoplasia | ?glandular neoplasia of endocervical type | Endocervical carcinoma in situ<br>Adenocarcinoma endocervical |
| | ?glandular neoplasia (non-cervical) | Adenocarcinoma: Endometrial Extrauterine<br>Not otherwise specified |
| Abbreviations: ? – suspected | | |

The current management protocols for cervical cytology are described in the third edition of the NHSCSP's colposcopy and programme management document (NHSCSP publication 20), and are outlined in table 2. Currently, people with samples which show high grade dyskaryosis or worse are referred to colposcopy. Where low grade dyskaryosis is seen, the residual cellular material collected during the cervical screen is used for hr-HPV testing to determine whether a colposcopy referral is required. This is part of the management protocol referred to as HPV triage. The use of the HPV test helps to identify people who are at the greatest risk of having abnormalities which may require further investigation and treatment. Where 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.

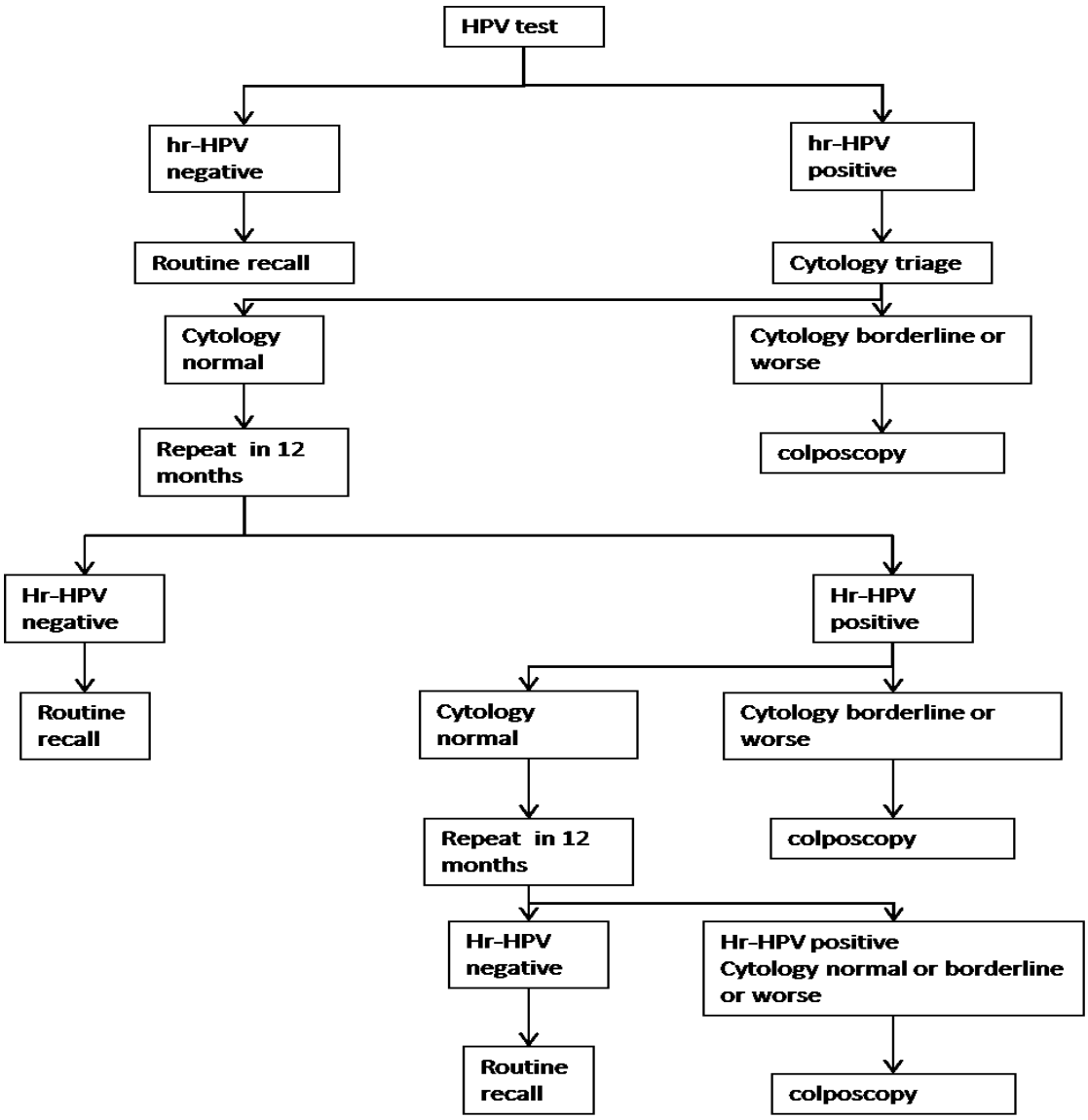
**Table 2 HPV triage management protocol**

| Result | Management recommendation |
|---|---|
| Inadequate - insufficient cells were available for analysis | Repeat in 3 months, refer to colposcopy after 3 consecutive inadequate samples. |
| Negative - adequate sample with no abnormal cells | Return to routine recall (3 or 5 years depending on age) |
| Borderline change in squamous cells | Test residual sample for high risk-HPV:<br>High risk-HPV detected – refer for colposcopy<br>High risk-HPV not detected – return for routine recall. |
| Borderline change in endocervical cells | |
| Low-grade dyskaryosis | |
| High-grade dyskaryosis (moderate) | Refer for colposcopy |
| High-grade dyskaryosis (severe) | Refer for colposcopy |
| High-grade dyskaryosis/?invasive squamous carcinoma | Refer for colposcopy |
| ?glandular neoplasia of endocervical type | Refer for colposcopy |
| ?glandular neoplasia (non-cervical) | Refer to gynaecology |
| Abbreviations: ? - suspected | |

Source: NHSCSP publication 20

An announcement from the Department of Health in July 2016 stated that HPV primary screening is to be rolled out in the NHS cervical screening programme. In HPV primary screening a cervical cytology sample is taken and sent to a laboratory but the sample is first tested for the presence of hr-HPV. The algorithm for the HPV primary screening pilots is shown below in Figure 1. In several sites in England, where HPV primary screening was piloted, it has now been adopted as the standard of care.

**Figure 1 HPV primary screening algorithm (pilot sites)**




Where HPV 16 and 18 genotyping tests are used people testing HPV 16 or 18 positive and cytology normal at baseline and again at their first 12 month follow up test can be referred to colposcopy without further repeat tests.

### *3.3.2 Colposcopy*

In 2014-15 there were 198,216 referrals to colposcopy clinics in England (Health and Social Care Information Centre, 2015), 66.8% of which were because of a cervical screening test result (45.6% borderline or low-grade dyskaryosis, 8% moderate dyskaryosis, 12.4% high grade dyskaryosis or worse) and 20.2% because there were clinical indications for the referral, for example abnormal bleeding. The remaining 14% were classed as referral for other reasons, which includes people who have had a normal cytology result

but HPV detected as part of the post treatment test of cure protocol (see section 3.3.4).

During a colposcopy the cervix is examined by a colposcopist using a colposcope, which is a low powered microscope. The aim of the colposcopy examination within the NHS Cervical Screening Programme (NHSCSP) is to confirm whether a potential abnormality identified by the cervical screening test is present, and if so to assess the likely extent and grade of the abnormal cells. The colposcopist applies solutions such as acetic acid or Lugol's iodine, to the surface of the cervix. These help to highlight any areas of abnormality on the cervical epithelium because normal and abnormal areas show different degrees of uptake of the solutions. NHSCSP publication 20 recommends that "where an adequate colposcopic examination has been conducted and the upper extent of the lesion and squamocolumnar junction visualised, the positive predictive value of a colposcopic diagnosis should be at least 65% for a high-grade lesion (CIN 2 or worse)".

### *3.3.3 Colposcopy management and treatment*

The treatment and management protocols for colposcopy services in England are described in the NHSCSP's colposcopy and programme management (NHSCSP publication 20) document. Of all people referred to colposcopy in England in 2014-15, 61.7% had a treatment or procedure at their first appointment. The most common procedure was diagnostic biopsy (47.7%), followed by an excision (12.2%), with the most common excision being a large loop excision of the transformation zone (LLETZ) (Health and Social Care Information Centre, 2015). Management is guided by a colposcopist's opinion of the extent of any abnormalities observed during the colposcopy examination. If an abnormality is identified, the colposcopist may take a diagnostic biopsy (punch biopsy) or 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 likely to be present. NHSCSP publication 20 recommends that treatment at first visit to colposcopy for a referral of borderline or low-grade dyskaryosis should not be offered.

NHSCSP publication 20 recommends that, unless an excisional treatment is planned (or done as part of see and treat), a diagnostic biopsy should be carried out when the cytology indicates high-grade dyskaryosis (moderate) or worse, and always when a recognisably atypical transformation zone is present. It also states that "low-grade cytological abnormality (low-grade dyskaryosis or less) and a low-grade or negative colposcopic examination do not require colposcopic biopsy if there is no atypical transformation zone present". In some circumstances, the NHSCSP publication 20 recommends that an excisional form of biopsy should be done:

- When most of the ectocervix is replaced with high-grade abnormality
- When low-grade colposcopic change is associated with high-grade dyskaryosis (severe) or worse
- When a lesion extends into the endocervical canal, sufficient cervical tissue should be excised to remove the entire endocervical lesion.

Biopsies are examined by a histopathologist and the results of the biopsy are used to help the colposcopist decide whether treatment is required. Typically, areas of CIN 2 or worse would require treatment. Treatment can be done either by excising the area of abnormal cells or by destroying them in situ (ablation). During an excision treatment cells are usually removed using a thin electrically-heated looped wire in a procedure called a large loop excision of the transformation zone (LLETZ). The excised tissue is sent to histopathology to confirm the extent of the abnormality and to guide further management. LLETZ is usually performed in the colposcopy clinic using local anaesthetic. Sometimes, particularly where glandular abnormalities are present (CGIN), a deeper excision called a cone biopsy is required which may be done under general anaesthetic. NHSCSP publication 20 makes the following recommendations on the depth of the excision:

- Type I cervical transformation zone; for treating ectocervical lesions, excisional techniques should remove tissue to a depth/length of more than 7mm, though the aim should be to remove <10mm in people of reproductive age.
- Type II cervical transformation zone; excisional techniques should remove tissue to depth/length of 10mm to 15mm depending on the position of the squamocolumnar junction within the endocervical canal
- Type III cervical transformation zone; excisional techniques should remove tissue to a depth/length of 15mm to 25mm.

NHSCSP publication 20 recommends that ablative treatments are only done when:

- The entire transformation zone is visible
- There is no evidence of glandular abnormality
- There is no evidence of invasive disease
- There is no major discrepancy between cytology and histology

Unlike excisional treatments, ablative treatments are not examined by a histopathologist as the destruction of the cells in situ mean that no tissue samples are available for histopathology. Ablative treatments include laser ablation, cryocautery and cold coagulation.

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. The treatment and management of cervical cancer is described in more detail in the NICE pathway on cervical cancer and in the SIGN guideline on the management of cervical cancer.

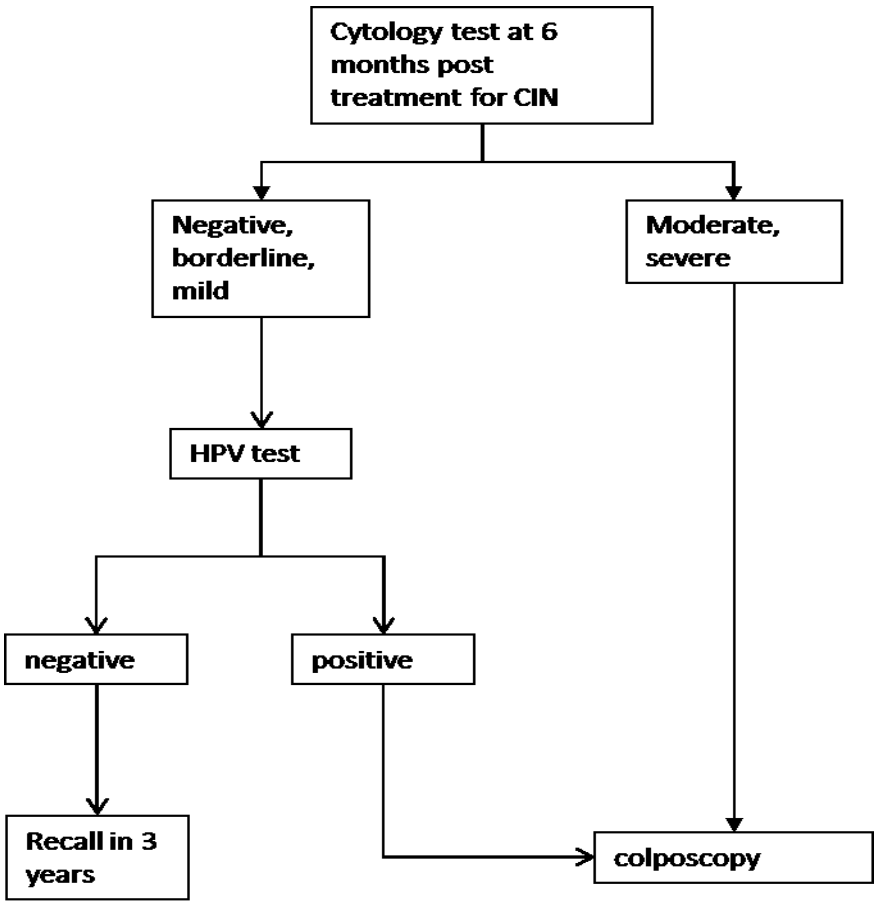
### *3.3.4 Follow-up after colposcopy*

Follow up after a colposcopy is dependent upon whether treatment has been done or whether surveillance of an abnormality has been recommended. Surveillance can often be done within the colposcopy service or within the community. NHSCSP publication 20 recommends that people referred with low-grade dyskaryosis or less and hr-HPV positive who have a satisfactory and normal colposcopic examination are at low risk of developing cervical cancer and can be returned to community-based recall. Those who have a colposcopically low-grade lesion may be followed up at 12 months in the colposcopy clinic or the community. If the lesion has not resolved within 2 years of referral to colposcopy a biopsy should be taken.

For people referred with high-grade dyskaryosis who do not have treatment, surveillance with colposcopy and cytology every 6 months is recommended even if colposcopy is normal. If the high-grade abnormality persists, excision treatment is recommended. For those with a colposcopically low grade lesion, multiple biopsies should be taken. Where CIN1 or less is confirmed, colposcopy and cytology at 6 months is advised. Follow up for people referred under the HPV primary screening algorithm is described in more detail in the NHS cancer screening programme's HPV primary screening pilot: colposcopy management recommendations algorithm.

For people who had treatment for CIN whilst under the care of their colposcopy team, follow up will comprise a cytology test 6 months after treatment with a reflex HPV test for people with low grade or normal cytology. This is known as the test of cure protocol, which is outlined below in figure 2. Test of cure differs under HPV primary screening, and is described in the NHS cancer screening programme's HPV primary screening pilot: colposcopy management recommendations algorithm.

**Figure 2 test of cure algorithm**




Adapted from NHSCSP publication 20

People who have been treated for CGIN will also have test of cure at 6 months post treatment; if this sample is reported as cytology normal and HPV not detected, a second test of cure sample will be advised in a further 12 months (18 months post treatment). If the second sample is cytology and HPV negative, discharge to recall in 3 years will be advised. People who have abnormal cytology or a HPV positive result at either scheduled test of cure should be referred back to colposcopy for further management.

## *4 Comparator*

The comparator for this assessment is conventional colposcopy. The colposcopy examination is described in more detail in section 3 above. The overall aim of a conventional colposcopy examination is to differentiate high grade lesions from low grade lesions to ensure that advanced disease is detected, but low grade lesions are not over treated. Conventional colposcopy is a subjective examination which may be associated with both intra- and inter-observer variability, particularly for low grade lesions which are often

more difficult to assess because they are associated with more subtle changes than high grade lesions.

## *5 Scope of the assessment*

**Table 3 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:<br>• The HPV triage screening algorithm (including test of cure), or<br>• The HPV primary screening algorithm recommended for use in the sentinel sites (including test of cure).<br><br>Where data permits the following subgroups may be considered:<br>• People with a hr-HPV infection caused by genotype 16.<br>• People with a hr-HPV infection caused by a non-16 genotype. |
| **Interventions** | • DYSIS with DYSIS map - this includes version 3, touch and ultra models<br>• ZedScan I<br>Both interventions are intended to be used in conjunction with a conventional colposcopy examination. |
| **Comparator** | • Conventional colposcopy alone |
| **Healthcare setting** | Colposcopy services in the NHS cervical screening programme |
| **Outcomes** | Intermediate measures for consideration may include:<br>• Diagnostic accuracy including sensitivity, specificity and predictive values<br>• Test failure rates<br>• Number of biopsies taken and diagnostic yield<br>• Number of treatments and treatment type<br>• Number of 'see and treats'<br>• Duration of colposcopy examination<br>• Number of people discharged from colposcopy |
| | Clinical outcomes for consideration may include: |

| | |
|---|---|
| | • Morbidity and mortality associated with treatment and biopsies<br>• Morbidity and mortality associated with cervical cancer |
| | Patient-reported outcomes for consideration may include:<br>• Pain and anxiety associated with the colposcopy examination, biopsies, treatment and waiting for results.<br>• Acceptability of the technologies and patient satisfaction.<br>• Health related quality of life |
| | Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include:<br>• Costs of the adjunctive colposcopy technologies including the cost of the devices, software and any consumables<br>• Costs of staff and associated training<br>• Medical costs arising from testing including ongoing care and follow up and histopathology costs<br>• 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 sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. |

## *6 Other issues for consideration*

It is difficult to obtain robust estimates of the diagnostic accuracy of colposcopy because in clinical practice it is unlikely to be considered ethical to take biopsies to confirm that no disease is present where the colposcopy examination is normal. Estimates of the accuracy of colposcopy therefore vary widely in the literature because the performance of colposcopy is driven by the prevalence of disease which varies according to whether population based cervical screening programmes are available, and if so which tests and management strategies they use.

Published data have suggested that cellular changes caused by HPV 16 may be more apparent on colposcopy examination than cellular changes caused by other hr-HPV genotypes (Jeronimo et al. 2007). It is therefore possible that

the accuracy of colposcopy, and the adjunctive technologies, may differ in subgroups of people with HPV 16 and with other hr-HPV genotypes. The relative sizes of these subgroups may change in the future as people who are vaccinated against HPV 16 and 18 enter the NHS Cervical Screening Programme. The HPV vaccination programme began in 2008 and is offered to girls aged 12 to 13 in the NHS childhood vaccination programme. Current uptake of the vaccination, that is administration of all recommended doses, is 86.1% (NHS England, 2014). Initially a catch up programme was offered for all girls aged up to 18 years. This cohort is now entering the NHS Cervical Screening Programme, but may not be fully protected against HPV 16 and 18. This could be because some of those who accepted the vaccination were already sexually active, and therefore had potentially been exposed to HPV 16 and 18. Further, uptake in the cohort was lower because some people were no longer in full time education making access to the vaccination more difficult, particularly as a 3 dose schedule was initially offered. The full impact of HPV vaccination on the screening programme is therefore not fully understood at present, and the prevalence of disease is likely to change over time as partially vaccinated and fully vaccinated cohorts enter screening and colposcopy services.

At the time of writing NICE diagnostics guidance 4, systematic reviews had been published on the longer term impacts of treatment on future obstetric outcomes (Arbyn et al. 2008 and Kyrgiou et al. 2006) but it was not certain whether these observed effects applied to the UK. Subsequent to the systematic reviews, the Pre-term delivery after Cervical Treatment (PaCT) study group have published several papers (Castañon et al. 2012; Castañon et al. 2014 and Castañon et al. 2015) from a cohort study within the NHS Cervical Screening Programme using record linkage between Hospital Episode Statistics data and hospital colposcopy and obstetric records to investigate the longer term impacts of treatment on pre-term birth in subsequent pregnancies in England.

## *7 Potential equality issues*

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

All people with cancer are covered under the disability provision of the Equality Act (2010) from the point of diagnosis. Cervical cancer may be more prevalent in certain ethnic groups.

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 occur in the cervix during pregnancy.

# *8 Potential implementation issues*

## 8.1 Clinician confidence

Some colposcopists may have a preference for conventional colposcopy. It is important to emphasise that the technologies would be used as an adjunct and not a replacement for conventional colposcopy because the skills and expertise of a colposcopist would still be required to aid the interpretation of 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.

## 8.2 Record management

The adjunctive technologies would need to have the ability 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.

## 8.3 Capacity

Centres that currently use the adjunctive colposcopy technologies often do not have a sufficient number for all colposcopists to use them at the same time. This leads to some people being assessed with conventional colposcopy alone whilst others also have an assessment with one of the adjunctive technologies.

## 8.4 Training

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

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January 2017

## Appendix A Glossary of terms

**Aceto-whitening**
A term used to describe the effect of acetic acid which stains proliferating epithelium (cells undergoing abnormal changes) white when applied to the cervix during a colposcopy examination.

**Cervical transformation zone**
The area of the cervix where the squamous cells that line the surface of the cervix and the glandular cells that line the cervical canal meet. Most abnormalities in cervical cells arise in this area, and this is the area of the cervix that is sampled during a cervical screening test and visualised in a colposcopy examination.

**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 occur 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 Papillomavirus (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 required.

## Appendix B Abbreviations

| | |
|---|---|
| CGIN | Cervical glandular intraepithelial neoplasia |
| CIN | Cervical intraepithelial neoplasia |
| HPV | Human papillomavirus |
| hr-HPV | High-risk human papillomavirus |
| LLETZ | Large loop excision of the transformation zone |
| NHSCSP | National Health Service Cervical Screening Programme |

## Appendix C References

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