National Institute for Health and Clinical Excellence

Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS and the Niris Imaging System

Issued: August 2012

NICE diagnostics guidance 4
www.nice.org.uk/dg4

Contents

1 Recommendations

1.1   DySIS is a clinically and cost-effective option, compared with standard
       colposcopy, for examining the uterine cervix in women referred for colposcopy,
       and should be considered in procurement plans for colposcopy equipment.

1.2   Current evidence is insufficient to determine whether the Niris Imaging System
       is a cost-effective option for use as a colposcopic adjunct for examining the
       uterine cervix in women referred for colposcopy.

2 The technologies

2.1   Two technologies, DySIS (DySIS Medical) and the Niris Imaging System (Imalux Corporation) were evaluated. DySIS comprises a digital video colposcope and dynamic spectral imaging technology that are used in combination with each other during clinical examination. The Niris Imaging System uses optical coherence tomography as an adjunct to a standard colposcope. Additional details are provided in section 4.

3 Clinical need and practice

The problem addressed

3.1   Colposcopy is an examination that allows a clinician to see the type and area of cervical abnormality, and decide if treatment is needed. Colposcopy occupies a key role in the prevention of cervical cancer by identifying pre-invasive or invasive lesions. However, the subjective nature of colposcopy means that it is prone to considerable inter- and intra-operator variation. The adjunctive colposcopy technologies included in this evaluation use objective and quantitative assessments.

3.2   The aim of this evaluation is to determine whether, in conjunction with current decision-making protocols, using adjunctive colposcopy technologies cost-effectively improves health outcomes and quality of life in women referred for colposcopy compared with using conventional colposcopy.

The condition

Epidemiology and incidence

3.3   Cervical cancer is the 12th most common cancer in women in the UK and accounts for around 2% of all cancers among women. In 2008, there were 2398 new cases diagnosed. In the UK, the lifetime risk of being diagnosed with cervical cancer has been estimated to be 1 in 134.

3.4   The incidence of cervical cancer varies with age. It is the most common cancer diagnosed in women younger than 35 in the UK (about 700 cases annually).

Prognosis

3.5   Women often develop changes in the cervix many years before any progression to cancer. These changes range from low-grade cervical intra-epithelial neoplasia (CIN 1), which is frequently not precancerous but can cause changes that can be detected at cervical screening, to high-grade CIN (CIN 2/3), which is more frequently precancerous.

3.6   Infection with certain genotypes of human papillomavirus (HPV), in particular HPV 16 and HPV 18 (high-risk HPV), have been shown to be associated with the development of cervical cancer and CIN; almost all cervical cancers contain high-risk HPV DNA. However, most HPV infections will not progress to CIN. Some cell changes associated with HPV will regress to normal. Certain risk factors are associated with the progression of HPV infection to CIN. These include the HPV genotype, early age at first sexual intercourse, long duration of the most recent sexual relationship and cigarette smoking.

The diagnostic and care pathways

3.7   The care pathway for this assessment was taken from the NHS Cervical Screening Programme guidelines 'Colposcopy and programme management' (2010) and 'HPV triage and test of cure implementation guide' (2011).

Diagnosis

3.8   In England, women are invited for regular cervical screening every 3 years (if aged between 25 and 49) or every 5 years (if aged between 50 and 64) under the NHS Cervical Screening Programme. Most screening is conducted using liquid-based cytology; a sample of exfoliated cells is brushed from the transformation zone of the cervix for assessment in a pathology laboratory. The transformation zone is the area of the cervix where columnar epithelium is converted to squamous epithelium by squamous metaplasia. It is the area where most abnormal change occurs. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryotic. The degree of dyskaryosis can range from mild to severe, or borderline changes may be seen.

3.9   The next step depends on cytology results and the presence or absence of high-risk HPV. According to the NHS Cervical Screening Programme guidelines, women with borderline or mild dyskaryosis on cytology who are also HPV positive should be referred for colposcopy (see 4.10–4.14 for information about colposcopy). Those with borderline or mild dyskaryosis on cytology who are HPV negative are returned to routine recall. Women who have 3 consecutive inadequate samples or who have a test result showing

moderate or severe dyskaryosis, possible invasion or possible glandular neoplasia, should be referred for colposcopy.

3.10   Once a colposcopic examination has been carried out, a diagnosis is made. This is based on colposcopy results, with or without histology results (from a biopsy that may be taken during the examination). Histological results are classified as normal, low-grade CIN, high-grade CIN or invasive carcinoma.

Management/treatment at or after colposcopy

3.11   Treatment and screening options include:

- Return to the NHS Cervical Screening Programme: if the whole transformation zone is visible and is normal, the woman is discharged and returned to routine cervical screening intervals (see section 3.8).

- Refer for re-screen: if no biopsy is taken at colposcopy the woman is returned to routine cervical screening intervals. If a biopsy is taken and shows CIN 1, the woman will have a cytological smear, with or without colposcopy, at 12 months.

- Diagnostic biopsy: a diagnostic biopsy is taken and sent to a laboratory for analysis. This is also known as a punch biopsy.

- Treatment biopsy: this involves removing the whole transformation area. It is called a treatment biopsy because by removing the transformation area, the clinician effectively treats the CIN. It is also known as excisional biopsy or large loop excision of the transformation zone. Excisional biopsy (taken during a colposcopy) combined with histology is the gold standard for detecting CIN.

- Treatment biopsy followed by cancer treatment: if histology results suggest cervical cancer, management can be either surgical (for example, radical hysterectomy, which involves the en-bloc removal of the uterus, cervix and upper vagina) or non-surgical (radiotherapy, chemotherapy or chemoradiotherapy).

3.12   According to the NHS Cervical Screening Programme guidelines, these management and treatment options are linked to the 4 possible outcomes of a colposcopic exam and histology as follows:

- Normal: if the whole transformation zone is visible and is normal, the woman should be discharged and returned to routine cervical screening intervals.

- CIN 1: if the woman is diagnosed with CIN 1, she should be placed under observation (to be treated only if regression does not occur after 24 months). However, depending on the woman's choice, CIN 1 can also be treated.

- CIN 2 or 3: if the woman is diagnosed with CIN 2 or 3, she should be offered treatment either by ablation or large loop excision of the transformation zone.

- Invasive carcinoma: if the woman is diagnosed with invasive carcinoma she should be referred for either surgical or non-surgical management.

3.13   There is variation in the management of moderate and severe dyskaryosis in women referred for colposcopy when evidence of dysplasia is seen on colposcopy. Some clinicians use a 2-appointment strategy, in which they take a punch biopsy in the first appointment and treat in the second. Other clinicians prefer a see-and-treat approach, in which the woman has a colposcopy examination and treatment in the same appointment.

Follow-up

3.14   The NHS Cervical Screening Programme recommends that women who have been treated for any grade of CIN should be tested for high-risk HPV to assess their risk of having residual or recurrent disease. This is known as test of cure and applies to all women attending their first post-treatment follow-up appointment or cytology test, and all women in annual follow-up after treatment for CIN. Test of cure means that if the cytology result after treatment is normal, mild or borderline, a test for high-risk HPV will be offered. If the test is negative the woman will not be recalled for a further 3 years. If high-risk HPV is found, however, she will be referred again for colposcopy and followed up in accordance with national guidelines. Women who have received treatment for cancer as opposed to CIN are not included in the test of cure protocol.

4 The diagnostic tests

DySIS

4.1   DySIS is a digital video colposcope that also uses dynamic spectral imaging to evaluate the blanching effect of applying acetic acid to the epithelium (acetowhitening). It produces a quantitative measurement of the rate, extent and duration of the acetowhitening. The dynamic map (DySISmap) produced can be overlaid on a colour image of the tissue to help the clinician determine the presence and grade of any lesion.

4.2   DySIS consists of an optical head with a white light-emitting diode for uniform illumination, and magnification optics coupled to a digital colour charged-coupled device camera for image capture. It also includes a computer and control electronics unit with a thin film transistor monitor for image and data display. Linear polarisers are used in both the imaging and illumination pathways to reduce surface reflection (which might obscure the acetowhitening effect). The optical head does not come into contact with the tissue. It magnifies images between 10 and 27 times. It is mounted on a mechanical arm to position and stabilise it, and locked onto an extension shaft attached to the speculum, to ensure a stable field of view during image acquisition. For this reason, the speculum used with DySIS is different from the standard specula used in colposcopy and gynaecology practice. The average duration of use per examination is less than 15 minutes.

4.3   In this assessment, DySIS was evaluated in 2 ways. It was first evaluated as a stand-alone test, in which only the DySISmap was used in decision-making. DySIS was also evaluated when DySISmap was used in conjunction with colposcopy (DySIS colposcopy). In the latter case, the most serious result from either test was taken as the result of the testing combination. However, because this latter approach is considered by both the manufacturer and the clinical advisers to be the way DySIS would be used in actual practice, only the results of that analysis are included here.

4.4   It is claimed that new users can be trained to use DySIS, and to interpret the DySISmap, in 2–4 hours. DySIS has a CE mark and the cost in the UK ranges

from £18,000 to £22,000. DySIS includes a colposcope and no additional scope is needed. Costs for specula are £3.50 per examination.

Niris Imaging System

4.5   The Niris Imaging System is a non-invasive device designed to aid in the detection and diagnosis of early-stage disease. It is used for guidance of biopsy and surgery, and in post-treatment surveillance in various clinical applications, one of which is as an adjunct to colposcopy. It uses optical coherence tomography, using near-infrared light to produce real-time, high-resolution, cross-sectional imaging of tissue microstructure.

4.6   The major claimed benefit of the Niris Imaging System is its ability to scan multiple layers of epithelial tissue. Niris provides an optical biopsy by visualising tissue microstructure to a depth of 1.6 mm.

4.7   The Niris device consists of an image-management console and docking station, a laptop computer user interface, a 2.7 mm front-viewing screen, flexible optical probe and accessories. The image acquisition and measurement tools are sufficiently fast to allow image data to be analysed in real time and at the site of care. According to the manufacturer, the average duration of use per treatment for Niris alone is 2 minutes.

4.8   Niris probes can be used for around 200 procedures, and may be processed for re-use. According to the manufacturer, the average duration of use per examination (Niris imaging system and colposcopy combined) is around 4 minutes. A disposable probe sheath can be used to provide physical stability and help prevent cross-contamination.

4.9   New users can be trained in around 2 hours. The Niris Imaging System costs US$49,500 (around £31,000) plus taxes and shipping. The probe costs US$2700 (around £1700) and a disposable sheath costs US$30 (around £19). A conventional colposcope is also needed when using Niris.

Comparator

4.10   Conventional colposcopy is the comparator in this evaluation. Colposcopy is an essential part of the NHS Cervical Screening Programme. The purpose of a colposcopic examination is to identify lesions in a cervix when an abnormality is already suspected because cervical cytology is known to be abnormal.

4.11   A colposcope is a low-power, stereoscopic, binocular field microscope with a powerful light source. It is used for magnified visual examination of the uterine cervix to help in the diagnosis of cervical neoplasia. During the examination, the features of the cervical epithelium are observed after the application of normal saline, 3–5% acetic acid (to look for acetowhitening) and Lugol's iodine in successive steps.

4.12   Acetowhitening is not unique to CIN and early cancer. It is also seen in other conditions, such as immature squamous metaplasia, healing epithelium (associated with inflammation), leukoplakia and condyloma. It is also seen in congenital transformation zones.

4.13   According to the NHS Cervical Screening Programme guidelines, 'Colposcopy and programme management' (2010), the predictive value (not defined, but presumably positive predictive value) of a colposcopic diagnosis of a high-grade lesion (CIN 2 or worse) should be at least 65%. The guideline also states that, 'colposcopists should be able to differentiate high-grade lesions (intra-epithelial or otherwise) from low-grade lesions in order to avoid missing advanced disease and to reduce overtreatment for low-grade lesions'.

4.14   The average purchase price of a colposcope is £10,000 and the maintenance cost is £1000 per annum. These prices were provided by clinical advisers during the assessment.

5 Outcomes

5.1   The Diagnostics Advisory Committee (appendix A) considered evidence from a number of sources (appendix B), primarily the assessment performed by the External Assessment Group.

How outcomes were assessed

5.2   The assessment consisted of a systematic review of the evidence on clinical-effectiveness data for the 2 technologies included in the evaluation and the comparator. The outcome measures included diagnostic test accuracy outcomes (sensitivity and specificity), adverse effects and patient experience. Other health outcomes such as morbidity and mortality from cancer and treatment were also modelled in the assessment.

5.3   A systematic review of the evidence on cost effectiveness for the 2 technologies was undertaken by the External Assessment Group. No economic evaluation studies of colposcopy or colposcopic adjuncts (DySIS or the Niris Imaging System) that met the inclusion criteria were identified.

5.4   An economic model was constructed to follow a linked evidence approach in which intermediate outcomes (results of the test/s) were linked to treatment outcomes and hence quality-adjusted life year (QALY) gains. Costs and QALYs were assigned to each of the 2 technologies and the comparator.

5.5   The analysis compared the new adjunct devices with standard colposcopy for examination of the uterine cervix to detect cancerous and precancerous cervical tissue in women referred for colposcopy through the NHS Cervical Screening Programme. The analysis provided a framework for the synthesis of data from the review of clinical effectiveness and other relevant parameters.

Clinical effectiveness

5.6   The studies that met the inclusion criteria in the clinical-effectiveness searches carried out by the External Assessment Group comprised 2 main published

studies of DySIS, 2 additional subgroup assessments, and 3 studies of the Niris Imaging System (all published in full).

5.7   There was considerable heterogeneity between the included studies in terms of patient characteristics and comparator technologies used, therefore the External Assessment Group did not undertake quantitative synthesis. Narrative synthesis was included for each adjunctive technology separately.

5.8   Because of the heterogeneity of the assessed studies, only 1 study of DySIS and 1 study of the Niris Imaging System were considered relevant for clinical practice, and were used by the External Assessment Group to inform the model.

DySIS

5.9   Both studies of the DySIS colposcope (Soutter et al. 2009 and Louwers et al. 2011) found a statistically significant higher sensitivity with DySIS than with conventional colposcopy for identifying CIN 2+ (CIN 2 or higher) disease. The paper used to inform the economic model (Louwers et al. 2011) reported the sensitivity of DySIS colposcopy to be 79.6% (95% confidence interval [CI] 71 to 86) compared with 51.9% (95% CI 43 to 61) for conventional colposcopy alone. However, specificity was clinically significantly lower with DySIS colposcopy at 62.6% (95% CI 54 to 70) compared with 81.7% (95% CI 74 to 87) for conventional colposcopy alone.

5.10   Women referred with low-grade cytology are more likely to have their condition managed on the basis of colposcopy results alone than women with high-grade cytology, who are more likely to have biopsies with less significant colposcopic findings. The sensitivity of DySIS remained high (77.4%) in the subgroup of women referred for colposcopy with low-grade cytology, whereas the sensitivity of conventional colposcopy was low in this subgroup (19.4%). This study (Soutter et al. 2010) used video colposcopy and was reported as a conference abstract only.

Niris Imaging System

5.11   Two studies of the Niris Imaging System (Escobar et al. 2006, Liu et al. 2010) did not categorise women by CIN stage but only by 'normal', 'abnormal' or 'indeterminate'. These studies were not considered usable for the assessment. One study of the Niris Imaging System (Gallwas et al. 2012) was the most relevant for clinical practice, because of the cut-offs used for categorising patients. This study reported that the Niris Imaging System had a lower sensitivity for identifying CIN 2+ disease than conventional colposcopy (86.5% compared with 99%) but a similar specificity (63.6% compared with 61%). In this study, only suspicious areas were biopsied, which raises doubt about the meaning of the sensitivity and specificity figures because false negative results cannot be determined. No reliable estimates of the sensitivity and specificity for identifying CIN 2+ could be determined from the assessed studies.

Economic analysis

Clinical outcomes

5.12   Modelling was used to estimate clinical outcomes. A model was constructed with 2 submodels. In the first submodel, a decision tree was developed to model the short-term diagnostic and treatment pathways and outcomes of women referred for colposcopy. In the model, women are first allocated according to their true underlying state, with distribution being dependent on their reason for referral. The decision tree models diagnostic and treatment pathways according to probabilities for diagnostic accuracy and treatment effectiveness.

5.13   In the second submodel, a Markov model (based on a model previously developed at the University of Sheffield) simulates the natural history of patients and captures future cytological screening and referrals to colposcopy to estimate outcomes of initial diagnoses and treatment choices. The natural history model consists of 9 states: clear, HPV, CIN 1, CIN 2/3, invasive cancer stages 1–4 and death. Women enter the natural history model in the state based on their outcome from the diagnostic and treatment decision tree. They progress and regress between these states every 6 months based on age-related transition probabilities.

Costs

5.14   An estimate of the average cost per procedure for each technology is determined by the set-up cost, annual recurring costs and per-patient costs. The set-up costs consist of the capital cost of the machine. The recurring costs consist of the annual maintenance costs and the costs involved in replacing equipment and overheads. Per-patient costs consist of the consumables used for each procedure and the cost of staff carrying out the investigation. The manufacturers provided the information used to estimate the costs for each technology and clinical advisers provided the purchase price and maintenance costs for colposcopy.

5.15   The purchase price of each technology was amortised over its expected lifetime. The equivalent annual cost was calculated from the purchase price of the technology and the useful life of the equipment, using a discount rate of 3.5%. The total cost per patient was estimated using an average of 1229 women examined per device per year. This average was estimated from the number of devices and the number of colposcopies undertaken in 3 clinics as reported by the clinical advisers.

5.16   The cost of a colposcope was added to the Niris Imaging System because in clinical practice colposcopy will be needed to guide the probe or to confirm diagnosis. Base-case costs per patient, including equipment, maintenance, and disposables were £3.50 for conventional colposcopy, £8.29 for DySIS colposcopy, and £40.26 for the Niris Imaging System.

Cost effectiveness

5.17   All analyses were conducted separately for each reason for referral and then a weighted average of cost effectiveness was reported across all reasons for referral.

5.18   Because of the lack of reliable evidence for the Niris Imaging System, the base-case analysis compared DySIS colposcopy with standard colposcopy. An indicative analysis was carried out for the Niris Imaging System.

DySIS

5.19   The base-case analysis compared DySIS colposcopy with standard colposcopy alone for each reason for referral. In all instances, standard colposcopy alone was dominated by DySIS colposcopy (that is, standard colposcopy was more expensive and less effective). For the whole population, based on a weighted average of the results of each reason for referral, DySIS colposcopy provided more QALYs (0.01466) at a lesser cost (£59.59). The base case indicates that DySIS colposcopy is a cost-effective form of management, given the assumptions and evidence used.

5.20   The base-case model demonstrated that an increase in test specificity for CIN 2+ resulted in decreased QALYs. This unusual situation results primarily from reductions in treatment for CIN 2 in women who in fact have CIN 1 rather than CIN 2. An increase in specificity means that more CIN 1 is correctly diagnosed and there are fewer mis-diagnoses of CIN 2. Because CIN 1 is not routinely treated, the model shows a decrease in QALYs and in doing so suggests that immediate treatment of women with CIN 1 improves health outcomes. However, this may reflect inputs to the model that do not capture the health disbenefits and cost of biopsy. Therefore, further sensitivity analyses were carried out to determine which inputs would have to change in the model so that an increase in specificity for CIN 2+ would increase QALYs. The levels of change needed are:

- the QALY decrement of treatment biopsy is increased from 0.005 to 0.13 (or 47.5 days of healthy life) **or**

- the cost of treatment biopsy is increased from £97 to £2758 **or**

- treatment patterns are modified to include treatment biopsy of CIN 1 for women referred with borderline or mild dyskaryosis.

5.21   Separate secondary analyses were undertaken for the scenarios in which the QALY decrement of treatment biopsy is 0.13 or the cost of treatment biopsy is £2758. The results showed that even if the QALY decrement for treatment biopsy is increased to levels at which test specificity improvements do not decrease QALYs, standard colposcopy is still dominated by DySIS colposcopy for the overall population and for most of the individual referral groups. DySIS

colposcopy was found to be less costly and less effective than standard colposcopy in women referred with possible neoplasia (the incremental cost-effectiveness ratio [ICER] for standard colposcopy was £303 per QALY gained) and in women who have had 3 inadequate cytology tests (the ICER for standard colposcopy was £32,009 per QALY gained).

5.22   A further sensitivity analysis was conducted to establish the QALY decrement of treatment biopsy that would result in DySIS colposcopy having an ICER greater than £20,000 per QALY gained compared with standard colposcopy. The results showed that the QALY decrement would have to be 0.42 (or 153 healthy days) for DySIS colposcopy not to be cost effective compared with standard colposcopy alone.

5.23   Increasing the cost of treatment biopsy to £2758 suggested that standard colposcopy alone was less costly and less effective than DySIS colposcopy in the overall population. DySIS colposcopy had an ICER of £12,761 per additional QALY. The sensitivity analysis of this secondary analysis showed that DySIS colposcopy has an ICER in the overall weighted population of less than £10,000 per QALY gained.

5.24   A further sensitivity analysis established that the cost of treatment biopsy would have to be £8912 for DySIS colposcopy not to be cost effective compared with colposcopy alone at £20,000 per QALY gained. At £30,000 per QALY gained, the cost of treatment biopsy would have to be £12,695 for DySIS colposcopy not to be cost effective compared with colposcopy alone.

5.25   The cost per QALY of DySIS colposcopy hinges on its increased sensitivity and the increase in the number of women treated. These 2 factors are the driving force behind DySIS colposcopy's dominance over standard colposcopy. Modifying other parameters only had minor effects on the cost per QALY of DySIS colposcopy.

5.26   Extensive sensitivity and scenario analyses were conducted on a variety of measures including the effectiveness of treatment biopsy on CIN 1. In all analyses, DySIS was either dominant or cost effective.

Niris Imaging System

5.27   No reliable estimates of the sensitivity and specificity of the Niris Imaging System for CIN 2+ were identified in the assessment, and a full economic analysis was therefore not possible. An indicative analysis of the Niris Imaging System was carried out based on its cost. Assuming the same specificity as DySIS colposcopy, the sensitivity of the Niris Imaging System would have to be 86% to be considered cost effective (compared with DySIS colposcopy). Although the reported sensitivity of the Niris Imaging System was higher in the 1 study examined, that study only biopsied areas considered abnormal by the Niris Imaging System, so the sensitivity is likely to be a significant overestimate.

6 Considerations

6.1   The Committee discussed a number of issues raised about the validity of the DySIS study included in the cost-effectiveness analysis. The Committee concluded that these issues did not substantially affect its use in the assessment. In addition, the External Assessment Group informed the Committee that the model was designed to reflect actual clinical practice even though the study could be considered an efficacy study.

6.2   The Committee heard from clinical experts that colposcopy practice in the Netherlands resembles that in the UK, and that therefore the accuracy of colposcopy in the DySIS study could be taken to represent the accuracy of colposcopy in NHS practice. The Committee was informed that the accuracy data on colposcopy in this study is similar to that from another study carried out in Hammersmith, London (even though the patient populations varied somewhat and, in the Dutch study, may have included women who would not be included in the NHS Cervical Screening Programme because of their age).

6.3   The Committee considered whether the model included the possibility of uninterpretable DySIS results and was informed that the modelling was conservative and used intention-to-treat results so that the impact of any uninterpretable results was included.

6.4   The Committee considered the issue of how increasing specificity of DySIS in the base-case model led to worse outcomes, suggesting that some of the benefits accrued arise from treating CIN 1. The External Assessment Group informed the Committee that this counterintuitive effect has been identified in previous literature. The Committee was informed that current NHS Cervical Screening Programme guidelines recommend that CIN 1 lesions should not be routinely treated immediately and are usually managed conservatively by a combination of cytology and colposcopy follow-up at between 6 and 12 months. The Committee was informed that this result may be caused by underlying assumptions in the base-case model such as the lack of downstream adverse effects from large loop excision of the transformation zone, the low disutility from large loop excision of the transformation zone and the comparatively higher disutility from colposcopy. The Committee concluded

that, in this instance, specificity is not critical because sensitivity analyses undertaken by the External Assessment Group showed the cost-effectiveness results to be robust to changes in the assumptions about the impact of false-positive test results.

6.5   The Committee considered how much weight the model places on the negative effects of biopsy. The Committee was informed that the long-term costs of large loop excision of the transformation zone had not been incorporated in the model and that this could potentially overestimate the advantage of DySIS. Although an existing meta-analysis indicates minimal long-term adverse results from large loop excision of the transformation zone, clinical experts informed the Committee that its long-term effects are still not well understood.

6.6   The Committee was informed that there is variation in the clinical practice of colposcopy in the NHS. The Committee considered the possible effects of this variation on the cost effectiveness of DySIS. The External Assessment Group informed the Committee that in order to explore this variation, the model was run with 2 sets of treatment probabilities, the first based on clinical guidelines and clinical advice, and the second based on treatment patterns from data about current clinical practice obtained from the Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead. DySIS was found to be cost effective in both analyses. Therefore, the Committee accepted that clinical practice does not substantially affect the cost effectiveness of DySIS. In addition, the Committee was informed that quality assurance measures currently being implemented in the colposcopy programme are expected to reduce the variation in clinical practice.

6.7   The Committee considered whether the additional time it takes for the DySIS map to appear during the examination would have any significant impact on clinicians and women. The Committee was informed that this issue is not important because acetowhitening is slow to appear in low-grade lesions and the time taken for acetowhitening to appear forms part of the total time taken to carry out a colposcopy examination.

6.8   The Committee discussed the failure-to-function rates exhibited in the evidence. The manufacturer informed the Committee that an earlier version of

DySIS was used in that study and that the current model is substantially more reliable.

6.9 The Committee considered whether because DySIS is a rigid system attached to the speculum it might be less flexible for seeing abnormally positioned or difficult-to-view cervices than conventional colposcopy. The Committee was informed that those who have used DySIS have not found problems in this respect. The manufacturer informed the Committee that 2–5% of cervices are difficult to view with either standard colposcopy or DySIS.

6.10 The Committee considered the effect of throughput on the cost effectiveness of DySIS, particularly the assumption in the model that each device is used on 1229 women per year. The External Assessment Group confirmed to the Committee that it had carried out a scenario analysis with as few as 250 women per device per year. The result showed that the cost effectiveness of DySIS is not sensitive to throughput. Moreover, the Committee was informed that throughput was unlikely to be changed much with DySIS.

6.11 The Committee concluded that the modelling of DySIS colposcopy showed that it is robustly cost effective (possibly even cost saving) when compared with conventional colposcopy.

6.12 The Committee discussed making a research recommendation for DySIS. It acknowledged that the lack of studies with populations broken down by specific groups (clear, CIN 1, CIN 2 and CIN 3, possible invasion and possible neoplasia) had made it difficult for the Committee to make decisions. The Committee also recognised that more information on the long-term consequences and costs of treatment biopsy would provide needed inputs into the decision about the most appropriate management of CIN 1 and hence the impact of the lower specificity of DySIS colposcopy. However, it felt that the outcomes of this research were unlikely to result in changes to the recommendation on DySIS.

6.13 The Committee discussed the External Assessment Group's rationale for excluding the Niris Imaging System study from the base-case analysis. The Committee considered why the Niris Imaging System study was considered to

be unreliable. The External Assessment Group informed the Committee that the main reason for excluding the Niris Imaging System study was because only sites that did not appear normal were biopsied, so there was a high risk of bias in the diagnostic accuracy of figures reported in the study.

6.14   The Committee was informed that because the existing evidence did not provide appropriate values for sensitivity and specificity, an indicative analysis of the Niris Imaging System was carried out based on its cost and assuming that it had the same specificity as DySIS colposcopy. The result of this analysis suggests that the sensitivity of the Niris Imaging System would have to be 86% to be considered cost effective (compared with DySIS colposcopy). The Committee noted that, currently, the cost of the Niris Imaging System greatly exceeds the cost of DySIS colposcopy. The Committee concluded that current evidence is not sufficient to determine whether the Niris Imaging System would be cost effective and that additional research on the Niris Imaging System could provide better evidence of its diagnostic accuracy and clinical utility.

6.15   The Committee considered possible equality impacts and noted that although the risk of cervical cancer can vary among groups, the selection of the type of colposcope was unlikely to be differentially beneficial for those groups.

7 Recommendations for further research

7.1   The Committee made no specific research recommendations. Although there is uncertainty about some aspects of the products and the currently available evidence, it was felt that additional research was not likely to change the recommendations in the near future.

8 Implementation

8.1   NICE intends to develop tools, in association with relevant stakeholders, to
help organisations put this guidance into practice.

9 Related NICE guidance

Published

- Laparoscopic radical hysterectomy for early stage cervical cancer. NICE interventional procedure guidance 338 (2010)

- Topotecan for the treatment of recurrent and stage IVB cervical cancer. NICE technology appraisal guidance 183 (2009)

- High dose rate brachytherapy for carcinoma of the cervix. NICE interventional procedure guidance 160 (2006)

- Guidance on the use of liquid-based cytology for cervical screening. NICE technology appraisal guidance 69 (2000)

10 Review

NICE updates the literature search at least every 3 years to ensure that relevant new evidence is identified. At the same time, NICE contacts product sponsors and other stakeholders about issues potentially affecting the value of the diagnostic technologies, including significant changes to the price of the product or the comparator. In addition to this, NICE may review and update diagnostics guidance at any time if significant new evidence becomes available.

Andrew Dillon

Chief Executive

NICE

August 2012

Appendix A: Diagnostics Advisory Committee 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 Ron Akehurst

Professor in Health Economics, School of Health & Related Research (ScHARR), University of Sheffield

Dr Trevor Cole

Consultant Clinical and Cancer Geneticist, Birmingham Women's Hospital

Dr Paul Collinson

Consultant Chemical Pathologist, St George's Hospital

Dr Sue Crawford

General Practitioner (GP) Principal, Chillington Health Centre

Professor Ian A Cree

Senior Clinical Advisor , NETSCC, EME

Professor Erika Denton

National Clinical Director for Imaging, Department of Health, Honorary Professor of Radiology, University of East Anglia and Norfolk & Norwich University Hospital

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Lisa Hall

Professor of Analytical Biotechnology, University of Cambridge

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Professor Noor Kalsheker

Professor of Clinical Chemistry, University of Nottingham

Dr Mark Kroese

Consultant in Public Health Medicine, PHG Foundation, Cambridge and UK Genetic Testing Network

Professor Dietrich Mack

Professor of Medical Microbiology and Infectious Disease, School of Medicine, Swansea University

Professor Adrian Newland (Chair)

Chair, Diagnostics Advisory Committee

Dr Richard Nicholas

Consultant Neurologist, Heatherwood and Wexham Park Hospitals

Ms Margaret Ogden

Lay representative

Dr Diego Ossa

Director of Market Access Europe, Novartis Molecular Diagnostics

Mr Stuart Saw

Director of Finance, North East London and the City PCTs

Dr Steve Thomas

Consultant Vascular and Cardiac Radiologist at Sheffield Teaching Hospitals Foundation Trust

Mr Paul Weinberger

CEO, DiaSolve Ltd, London

Mr Christopher Wiltsher

Lay representative

Specialist Committee members

Dr Karin Denton

Consultant in Cellular Pathology

Mrs Phyllis Dunn

Clinical Lead Nurse

Dr Andrew Fish

Consultant Gynaecological Surgeon

Dr Sadaf Ghaem-Maghami

Clinical Senior Lecturer and Honorary Consultant in Surgical Gynaecological Oncology

Dr Pierre Martin-Hirsch

Consultant Gynaecological Oncologist

Mr Robert Music

Lay representative

Mr Charles Redman

Consultant Gynaecological Oncologist

Dr Miren Turner

GP/Colposcopist

NICE project team

Each diagnostics assessment is assigned to a team consisting of 1 Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Farouk Saeed

Technical Analyst

Hanan Bell

Technical Adviser

Jackson Lynn

Project Manager

Appendix B: Sources of evidence considered by the Committee

The diagnostics assessment report for this assessment was prepared by CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York:

- Wade R, Spackman E, Corbett M et al. Adjunctive colposcopy technologies for examination of the uterine cervix – DySIS, LuViva Advanced Cervical Scan and Niris Imaging System. February 2012.

Registered stakeholders

Registered stakeholders were recruited from the following organisations but do not necessarily represent the views of that organisation. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report and the diagnostics consultation document:

Manufacturers/sponsors:

- DySIS Medical (DySIS)

- Guided Therapeutics (LuViva Advanced Cervical Scan)

- Imalux Corporation (Niris Imaging System)

- Zilico Limited

Professional/specialist and patient/carer groups:

- British Society for Colposcopy and Cervical Pathology

- Jo's Cervical Cancer Trust

- NHS Cancer Screening Programme

About this guidance

NICE diagnostics technologies guidance is designed to help the NHS adopt efficient and cost effective medical diagnostic technologies more rapidly and consistently.

The programme concentrates on pathological tests, imaging, endoscopy and physiological measurement, since these represent most of the investigations performed on patients. The types of products which might be included are medical diagnostic technologies that give greater independence to patients, and diagnostic devices or tests used to detect or monitor medical conditions. Diagnostic technologies may be used for various purposes: diagnosis, clinical monitoring, screening, treatment triage, assessing stages of disease progression, and risk stratification.

This guidance was developed using the NICE diagnostic technologies guidance process.

We have produced a summary for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Changes since publication

December 2012: NICE Accreditation logo added

Your responsibility
This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, 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.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Copyright

Contact NICE

National Institute for Health and Clinical Excellence

Level 1A, City Tower, Piccadilly Plaza, Manchester M1 4BT

www.nice.org.uk

nice@nice.org.uk

0845 033 7780