NHS Cervical Screening Programme

NHS
Cancer Screening Programmes

# Achievable standards, Benchmarks for reporting, and Criteria for evaluating cervical cytopathology

Third edition including revised performance indicators

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# ACHIEVABLE STANDARDS, BENCHMARKS FOR REPORTING, AND CRITERIA FOR EVALUATING CERVICAL CYTOPATHOLOGY

*Third edition including revised performance indicators*

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*In July 2011 the British Society for Clinical Cytology and the National Association of Cytologists merged to form the British Association for Cytopathology.

# 1 INTRODUCTION

The NHS Cervical Screening Programme (NHSCSP) is widely recognised to be one of the most successful cancer prevention programmes in the world. Following the implementation in 1988 of a comprehensive, quality-assured, cytology-based programme, there has been a progressive decline in the incidence of, and mortality from, cervical cancer in England.

The provision of guidance on cytology reporting has been pivotal to the success of the programme, ensuring that standards are upheld and that rigorous evaluation and quality assurance take place. These standards were first outlined in 1995, with the publication of *Achievable standards, Benchmarks for reporting, and Criteria for evaluating cervical cytopathology* (ABC), a document that was subsequently revised and expanded in a second edition, published in 2000.[1]

The last decade has witnessed major changes to the NHSCSP. These include the introduction and national implementation of liquid-based cytology (LBC) sampling, and the implementation of high-risk human papillomavirus (HR-HPV) testing for triage of borderline and low-grade abnormalities and test of cure. Consequently, the NHSCSP and the Royal College of Pathologists have agreed that an updated version of the ABC guidance is required. That revision is presented here.

The principal changes introduced in this document are as follows:

- The NHSCSP will adopt the revised British Society for Clinical Cytology (BSCC) terminology for reporting cervical cytology:
  - Division of the category 'borderline change' into 'squamous' and 'endocervical' categories.
  - Division of dyskaryosis into 'low-grade' and 'high-grade' categories (the latter encompassing moderate and severe dyskaryosis).
  - Division of glandular neoplasia into 'endocervical' and 'non-cervical' categories.
- Guidance on the management of abnormal cytology results has been linked to this terminology:
  - Management guidance has been updated in the light of HR-HPV testing for triage of low-grade cytological abnormality and test of cure.
  - Expanded codes have been developed for standard cytology results to take account of the changes outlined above.
  - Performance indicators for evaluating cervical cytopathology have been expanded. They now include the referral value, the mean cervical intraepithelial neoplasia (CIN) score (MCS), the abnormal predictive value (APV), and the HR-HPV-positive rate for borderline/low-grade samples.

All of these changes are described in the chapters that follow.

# 2 ADEQUACY OF CERVICAL CYTOLOGY SAMPLES

Cytology practitioners disagree on the criteria for assessing the adequacy of a liquid-based cervical sample. For the purposes of these guidelines, an adequate liquid-based sample is defined as one that contains the minimum level of squamous epithelial cellularity necessary to ensure a squamous abnormality detection rate equivalent to that offered by conventional smears.

In the USA, where cytology practitioners have had more extensive experience of LBC than their UK counterparts, the Bethesda terminology system[2] requires a minimum of 5000 well-preserved and well-visualised squamous cells for a liquid-based preparation to be deemed 'satisfactory'. This figure is based on limited evidence,[3,4] and one study has reported a higher detection rate of high-grade lesions in LBC preparations with more than 20 000 cells. However, this study did not determine the influence of specimen cellularity on false negative rates.[5]

Following the national implementation of LBC, most UK laboratories have adopted a figure of up to 15 000 cells to define adequacy. This is based on manufacturers' guidance and the experience of the LBC pilot sites. However, a study to determine the minimum cellular requirements for the reliable assessment of liquid-based cervical cytology samples is in progress, funded by the National Institute for Health Research Health Technology Assessment programme.[6] The definition of adequacy may be modified when the results of this study are available.

## 2.1 Scanty samples

In some cases, a scanty sample will be sufficient to allow an abnormal cytology report to be issued, but may be inadequate to provide a reliable HR-HPV test result. Scanty samples that show no abnormalities should not ordinarily be tested for HPV.[7] When planning further action, it is important to be mindful of the effect of low cellularity on the reliability of cytology results (see sections 4.3 and 4.4).

# 3 REPORTING AND CLASSIFICATION OF CERVICAL CYTOLOGY

## 3.1 Introduction

Historically, the UK has used the BSCC (1986) classification to report cervical cytology. Elsewhere, other classifications are used, notably the Bethesda Classification (TBS).

In 2001, the BSCC began revising its classification, and the document that resulted from that process provides detail and images that may be useful to readers of this publication. However, the developments outlined in the introduction now necessitate further alterations. This document therefore outlines a new classification for abnormal cervical cytology, as agreed by the NHSCSP and the British Association for Cytopathology.

Table 1 summarises the main changes in terminology.

**Table 1** Summary of changes to terminology

| Previous terminology (BSCC 1986) | New terminology | Result code | Section |
|---|---|---|---|
| Borderline change | Borderline change in squamous cells | 8 | 3.10 |
| | Borderline change in endocervical cells | 9 | 3.11 |
| Mild dyskaryosis | Low-grade dyskaryosis | 3 | 3.5.1 |
| Borderline change with koilocytosis | | | |
| Moderate dyskaryosis | High-grade dyskaryosis (moderate) | 7 | 3.5.2 |
| Severe dyskaryosis | High-grade dyskaryosis (severe) | 4 | 3.5.3 |
| Severe dyskaryosis ?Invasive | High-grade dyskaryosis/?invasive squamous carcinoma | 5 | 3.7 |
| ?Glandular neoplasia | ?Glandular neoplasia of endocervical type | 6 | 3.8 |
| | ?Glandular neoplasia (non-cervical) | 0 | 3.9 |

## 3.2 Inadequate (result code 1)

Criteria for the determination of specimen adequacy are provided in Chapter 2. In addition, a sample must be reported as inadequate if the sample-taker has not completely visualised the cervix, or if the sample has been taken in an inappropriate manner, e.g. with a sampling device that has not been approved by the NHSCSP.

Samples must not be reported as inadequate if they contain any evidence of borderline change or dyskaryotic cells.

## 3.3 Negative (result code 2)

Adequate samples with no abnormal cells are classified as negative.

Samples may be reported as negative if they are classified as 'no further review' after scanning with the BD FocalPoint Slide Profiler, subject to the provisions of separate NHSCSP guidance.[8]

## 3.4 Definition of dyskaryosis

The primary requirement for identification of dyskaryosis is an abnormal chromatin pattern.

Features such as abnormal nuclear outlines or raised nuclear : cytoplasmic ratios may create a strong suspicion of dyskaryosis, but are insufficient for definitive diagnosis in the absence of an abnormal chromatin pattern. Detailed definitions of abnormal chromatin and other features can be found in BSCC guidance.[9]

## 3.5 Grading squamous dyskaryosis

The grade of dyskaryosis is defined by determining the ratio of nuclear diameter to cytoplasmic diameter.[9,10]

### *3.5.1 Low-grade dyskaryosis (result code 3)*

This is indicated by the presence of dyskaryotic cells with a nuclear : cytoplasmic diameter ratio of <50%. Such cells may also show koilocytosis, indicated by the presence of a large, sharply defined, clear perinuclear halo, surrounded by a condensed rim of cyanophilic or eosinophilic cytoplasm. However, the presence of koilocytosis or other morphological features of HPV infection should not be described in the report, as this introduces confusion when molecular tests for HR-HPV are also employed.

### *3.5.2 High-grade dyskaryosis (moderate) (result code 7)*

This should be used when dyskaryotic cells are present with a nuclear : cytoplasmic diameter ratio of >50%. Distinguishing precisely between high-grade dyskaryosis (moderate) and high-grade dyskaryosis (severe) is difficult and not entirely reproducible. However, if the nuclear : cytoplasmic diameter ratio is felt to be <75%, high-grade dyskaryosis (moderate) should be reported.

### *3.5.3 High-grade dyskaryosis (severe) (result code 4)*

This should be used when dyskaryotic cells are present with a nuclear : cytoplasmic diameter ratio of no less than 50%, and probably >75%.

### *3.5.4 Difficulties in grading dyskaryosis*

- When the cells and their nuclei are not circular, the nuclear : cytoplasmic diameter ratio will depend on the axis of measurement. In this case, the axis that produces the maximum nuclear : cytoplasmic ratio should determine the grade.
- There may be rare occasions when dyskaryosis is present but cannot be graded. This usually occurs where cytoplasm has been lost due to severe cytolysis or atrophy or where cell boundaries cannot be seen. Such cases should be coded as high-grade dyskaryosis (moderate) and a free text explanation should be provided.

## 3.6 Difficulties in the identification of dyskaryosis

- *Scanty abnormal cells* The presence of just one abnormal cell is sufficient for a report of abnormality. Sometimes dyskaryotic cells can be extremely sparse, and careful screening is required to identify such cases. Despite this, there is currently no evidence supporting the idea that a threshold for dyskaryosis exists, below which screening is less likely to detect abnormal cells in LBC samples.
- *Hyperchromatic crowded cell groups (HCCGs)* Care must be taken to examine all HCCGs to differentiate between abnormalities (which may be squamous or glandular), normal cells (including endometrial and endocervical cells), and normal changes (including metaplastic and atrophic changes, as well as repair and regeneration).
- *Pale cell dyskaryosis* Dyskaryotic cell nuclei stain to varying intensities, but truly pale dyskaryosis is not seen in LBC samples to the same extent as in conventional smears. Dyskaryosis is therefore defined by chromatin pattern and distribution, not by degree of staining intensity.
- *Bland dyskaryosis* The chromatin pattern in bland dyskaryosis appears only slightly abnormal (usually a degree of hyperchromatism is present). Cells are arranged in groups with abnormal architecture.[11]
- *Small cell severe dyskaryosis* A monotonous population of cells, showing an abnormal chromatin pattern, is present. The nuclear diameter of an affected cell is no more than twice that of a neutrophil polymorphonuclear leucocyte. Unless care is taken to identify the cell type, small cell severe dyskaryosis can be mistaken for immature metaplastic squamous cells, endometrial cells, or histiocytes.

Care should be taken to distinguish the following cell types and conditions from dyskaryosis:

- Follicular cervicitis.
- Changes caused by the herpes simplex virus.
- Endometrial or endometrioid cells.
- Lower uterine segment sampling (this can be a particular problem in women who have been treated by trachelectomy).
- Metaplastic cells.
- Changes of repair and regeneration.

## 3.7 High-grade dyskaryosis/?invasive squamous cell carcinoma (result code 5)

There are several recognised features:

- Well-differentiated, keratinising disease presents with bizarre keratinised cells, fibre and tadpole cells, and keratinised cytoplasmic debris.
- Poorly-differentiated carcinomas do not show these features, but are characterised by marked variation in cellular shape and size, an especially coarse granular chromatin pattern, and an altered chromatin distribution that results in nuclear 'windowing' or translucencies.
- A malignant diathesis is uncommon. When present, it is characterised by small collections of thin proteinaceous material with accompanying fragments of leucocytes and red blood cells. In SurePath this tends to be grey/blue in colour and is often closely associated with the malignant cells (hence it is known as 'clinging diathesis'). In ThinPrep preparations, lysed blood, which is always a component of diathesis, tends to be located around the periphery of the deposit, and may appear red in colour. Other fragments of debris may be distributed throughout the specimen.

## 3.8 ?Glandular neoplasia of endocervical type (result code 6)

Samples should be reported as '?glandular neoplasia of endocervical type' if they show cytological features suggestive of cervical glandular intraepithelial neoplasia (CGIN) or endocervical adenocarcinoma.[9]

The presence of a background diathesis in these samples normally suggests invasion, but caution should be exercised as the cytomorphological features of high-grade CGIN and early endocervical adenocarcinoma overlap.

Features of a malignant diathesis are described in section 3.7, above.

### *3.8.1 Differentiating high-grade squamous dyskaryosis and glandular neoplasia*

It may be difficult to distinguish these abnormalities from one another, and both may be present in the same sample. One factor favouring a report of glandular neoplasia is the presence of HCCGs with radial architecture and loose edges. The presence of HCCGs with tightly defined edges and a lack of architectural organisation favours a report of high-grade squamous dyskaryosis.

Ideally, the two types of abnormality should be distinguished from one another, but this may not be possible as some groups do not show clear features of either squamous dyskaryosis or glandular neoplasia. Fortunately, the adverse effects on patient management are minimal, as prompt colposcopy occurs after detection of either abnormality.

## 3.9 Glandular neoplasia (non-cervical) (result code 0)

Cytologically, cells from adenocarcinoma may present singly, in small clusters (including acinar or papillary formations), as highly vacuolated groups, and/or in HCCGs. Nuclear morphology varies from the relative uniformity of well-differentiated carcinomas to the highly pleomorphic nuclei of high-grade undifferentiated tumours.[9] Features supporting a diagnosis of endometrial, ovarian, or metastatic lesions from beyond the genital tract may be seen, and should be described in free text.[9]

It is extremely important to distinguish these cases from endocervical glandular abnormalities as the two are managed very differently: non-cervical glandular abnormality requires urgent referral for a gynaecological opinion, not colposcopy.

### *3.9.1 Difficulties in the identification of non-cervical glandular neoplasia*

- *Changes associated with intrauterine contraceptive devices (IUCDs)* include clusters of highly vacuolated cells. These clusters are usually few in number, and the cells show minimal nuclear atypia, and have thin-walled, punched-out vacuoles that may contain ingested but intact polymorphs. Occasionally it can be difficult to distinguish between such groups and vacuolated forms of adenocarcinoma, as both types of abnormality show coalescent, debris-filled, vacuolated cytoplasm. However, the nuclear pleomorphism that characterises adenocarcinoma is a useful distinguishing feature.
- *Psammoma bodies* in a cervical sample are a rare but potentially sinister finding, warranting appropriate investigations to exclude neoplasia of the female genital tract or peritoneum. Malignancy is most likely to be found in women who have atypical cells in the sample, are over 45 years of age, and are symptomatic. In the absence of definite cytological atypia, reactive processes such as chronic endocervicitis, endometritis, or IUCD effect should be included in the differential diagnosis. Although such a slide is technically negative for the purpose of cervical screening, the sample-taker should be informed of the differential diagnosis in free text, so that appropriate clinical management can be planned.
- *Endometrial cells* are commonly identified in conventional smears and LBC specimens, despite general acceptance of the fact that both sampling methods have a low sensitivity for detecting endometrial disease. The cytological features of any endometrial cells must be assessed in order to determine their potential clinical significance and to guide appropriate management (see Appendix 1).

## 3.10 Borderline change in squamous cells (result code 8)

The term ‘borderline change’ describes morphological alterations to squamous cells that fall short of low-grade dyskaryosis but that cannot be identified with certainty as the consequence of inflammatory, reactive, metaplastic, or hormonal processes. It is most important to examine borderline samples carefully, to ensure that dyskaryosis is correctly reported.

Cells showing borderline change form a distinct population that can be differentiated from surrounding cells of the same type. Cytological changes suggestive of HPV infection may be present, but the cells will lack either sufficient nuclear abnormality or koilocytosis to justify a report of dyskaryosis. The abnormal cells may be binucleate, and the nuclei may be enlarged, pyknotic, or show slightly irregular membranes. Cells showing borderline change can also be dyskeratotic, forming either orangeophilic sheets or clumps with intracytoplasmic keratin.

The category of 'borderline change: high-grade dyskaryosis not excluded' has been in widespread use in the UK and is broadly similar to the Bethesda category 'atypical squamous cells suggesting high-grade squamous intraepithelial lesion (ASC-H)'. However this category will be rendered obsolete by the use of HR-HPV triage.

### *3.10.1 Difficulties in the identification of borderline change in squamous cells*

- Dyskeratosis should not be confused with parakeratosis in cells with normal nuclei. Parakeratotic cells may form small 'rafts' or 'pearls', and these should not be reported as borderline groups. Additionally, orangeophilic cells with small pyknotic nuclei and a low nuclear : cytoplasmic ratio may be seen in atrophic samples, and care should be taken to distinguish these from cells showing borderline change.
- Inflammation, sometimes associated with atrophic vaginitis, non-specific cervicitis, or endocervical polyps, may increase the nuclear : cytoplasmic ratio, making cells appear immature. Where the nuclear : cytoplasmic ratio is high, suspicions of high-grade dyskaryosis may be aroused. However, as previously noted, a high nuclear : cytoplasmic ratio is not sufficient to diagnose dyskaryosis. Inspection of the chromatin should allow a confident diagnosis of inflammatory changes to be made.
- Even in the absence of features suggesting inflammation or repair, metaplastic squamous cells may show hyperchromatic, clumped chromatin. This mimics dyskaryosis, but may be degenerative in nature. Dyskaryosis in metaplastic cells will almost always be high grade, according to the grading criteria. Attention to the whole cell is important, as the cytoplasmic features that typify immature metaplasia tend not to be found in cases of true dyskaryosis.
- Atrophic changes are seen as sheets of parabasal cells with a relatively high nuclear : cytoplasmic ratio, due to loss of oestrogenic cytoplasmic maturation. Clumped chromatin, which mimics dyskaryosis, may be present, and cells may appear either as separated parakeratotic entities or as HCCGs. These cells should be assessed in relation to the slide as a whole, as dyskaryotic cells usually form a separate population that is distinguishable from the background cell pattern.

## 3.11 Borderline change in endocervical cells (result code 9)

Borderline change in endocervical cells was recognised in the BSCC 1986 classification, and has subsequently been incorporated into NHSCSP management guidelines. As with borderline change in squamous cells, the diagnosis should be used when dyskaryosis cannot be excluded. However, cases meeting the criteria for glandular neoplasia should be reported as such.

Typically, cell groups show either architectural or nuclear features suggesting CGIN. For example, there may be crowded cells with pseudostratification but little nuclear abnormality, or coarsely clumped chromatin with entirely normal architecture.

Borderline change in endocervical cells should be a rare diagnosis. The application of objective criteria and consensus reporting are recommended to maintain the specificity of the category and avoid unnecessary colposcopy.

### *3.11.1 Difficulties in the diagnosis of borderline change in endocervical cells*

- Cervicitis and polyps can produce reactive changes in endocervical cells, and these may mimic glandular neoplasia. However, inspection of both the architecture and the nuclear features of the groups, as described in sections 3.8 and 3.9, should exclude neoplasia in most cases, allowing a confident negative diagnosis.
- Most cases of tuboendometrioid metaplasia (TEM) and lower uterine segment sampling (LUS) should be confidently recognised and reported as negative. However, there may be occasions on which HCCGs mimic either high-grade squamous dyskaryosis or (less commonly) glandular neoplasia. A diagnosis of ‘borderline change in squamous cells’ or ‘borderline change in endocervical cells’ is appropriate to these situations. HR-HPV triage will reliably exclude significant disease.
- As there is no consensus on the category of borderline change in endometrial cells, this must not be used.[12]

# 4 RECOMMENDATIONS FOR MANAGEMENT

## 4.1 Management categories

Every cervical cytology report should carry a recommendation for subsequent management. There are four categories:

- Routine recall (or automatic ceasing from recall after the age of 65).
- Repeat cytology.
- Referral to colposcopy (standard or urgent).
- Referral to gynaecology (always urgent within the NHSCSP).

## 4.2 Inadequate samples and repeat cytology

Where an initial sample is inadequate, cytology should be repeated. The repeat sample should not be taken less than three months after the previous test. Women should be referred for colposcopy after three consecutive inadequate samples. Consideration should be given to investigating and treating any infections that are present after the second inadequate sample.

## 4.3 Borderline change (in squamous/endocervical cells) and HR-HPV triage

When borderline change in squamous or endocervical cells is reported on a cytology sample, a reflex HR-HPV test will be performed to assess the presence of HR-HPV DNA. Women who have borderline change of either type and who are positive for HR-HPV must be referred for colposcopy. Women who are HR-HPV negative are returned to routine recall.

Where a sample is scanty, HR-HPV testing may be attempted, but should only be considered reliable where the result is positive or when the validity of a negative result is confirmed by an internal control. In scanty samples in which cytology is reported as borderline and the HR-HPV result is negative, a further sample should be taken in six months, and the woman should be managed as follows:

- If the cytology report from the second screen is negative, borderline, or low-grade, an HR-HPV test should be conducted. Women with a positive HR-HPV test should be referred to colposcopy. Women with a negative HR-HPV test return to routine recall.
- If this second screen is reported as high-grade dyskaryosis (moderate) or worse, the woman should be referred straight to colposcopy.

## 4.4 Low-grade dyskaryosis and HR-HPV triage

When low-grade dyskaryosis is reported on a cytology sample, a reflex HPV test will be performed to assess the presence of HR-HPV DNA. Women who have low-grade dyskaryosis and who are positive for HR-HPV must be referred for colposcopy. Women who are HR-HPV negative are returned to routine recall.

In the case of a scanty sample, HR-HPV testing may be attempted, but should only be considered reliable where the result is positive or when the validity of a negative result is confirmed by an internal control. In cases involving a scanty sample in which cytology is reported as low-grade, and the HR-HPV result is negative and confirmed by an internal control, the woman can be returned to routine recall. However, if the HR-HPV test result is not confirmed by an internal control in this scenario, the woman should be referred straight to colposcopy.

### 4.5 High-grade dyskaryosis (moderate)

Women must be referred for colposcopy after one test is reported as high-grade (moderate) dyskaryosis. If women are not referred directly to colposcopy, the GP must make an urgent referral through the 'two-week wait' pathway.

### 4.6 High-grade dyskaryosis (severe)

Women must be referred for colposcopy after one test is reported as high-grade (severe) dyskaryosis. If women are not referred directly to colposcopy, the GP must make an urgent referral through the 'two-week wait' pathway.

### 4.7 High-grade dyskaryosis/?invasive squamous cell carcinoma

Women must be referred for colposcopy after one test is reported as high-grade dyskaryosis/?invasive squamous cell carcinoma. If women are not referred directly to colposcopy, the GP must make an urgent referral through the 'two-week wait' pathway.

### 4.8 Glandular neoplasia

When glandular neoplasia has been reported, the referral pathway will depend on the details provided about the source of the abnormal glandular cells (see Appendix 1).

- In cases in which the abnormal glandular cells probably originated from the endocervix, or the source is not specified, the woman must be referred for colposcopy. If a woman is not referred directly, the GP must make an urgent referral through the 'two-week wait' pathway.
- In cases in which the source of the abnormal glandular cells is likely to be a gynaecological site other than the endocervix, or metastasis from a non-gynaecological site (i.e. breast or large bowel), the woman should be referred to a gynaecology clinic. If a woman is not referred directly, the GP must make an urgent referral through the 'two-week wait' pathway.

Referrals to gynaecology clinics are not part of the screening programme and should be managed according to local protocols. The following guidance should be followed to ensure appropriate management.

- The woman's individual circumstances must be considered holistically. A referral combining cervical and extra-cervical investigations may be feasible in some cases (see section 6.3). Communication with the woman's GP may be advisable to avoid causing distress if the woman is already under treatment for the suspected condition.

- A member of the consultant medical staff at the cervical cytology laboratory must decide on the types and priorities of referrals required and ensure that each referral is made in a timely manner. Note that gynaecological referrals will not be covered by programme-wide failsafe systems.
- Arrangements must be made to inform the woman of her diagnosis of non-cervical glandular neoplasia. Such communications are particularly sensitive, as the woman may have received a screening result letter referring to a negative, borderline, or low-grade cytological abnormality.

## 4.9 Colposcopy

Colposcopy is a continuation of the screening process, providing further evidence about the nature of observed changes. The colposcopist must therefore have sight of the cytology report at the time of the examination.

Those reporting abnormal cervical cytology samples should be aware that women with reports indicating high-grade dyskaryosis or worse (including ungraded dyskaryosis) may be treated by excision biopsy at first colposcopic examination, if an appearance consistent with a high-grade abnormality is seen. However, when colposcopic referral results from a report of low-grade dyskaryosis or borderline change (usually on first occurrence), or from an inadequate sample, treatment may well be deferred until results from a histological biopsy are obtained, particularly when the colposcopist has not seen any cervical abnormality.

Those reporting abnormal cervical cytology samples may refer a woman for colposcopic assessment when cytological changes are difficult to interpret. In these instances, colposcopic appearances may also be non-specific, but a more accurate assessment is likely to be obtained by combining cytological review, colposcopic appearances, and histological biopsy of any abnormality seen. Ideally, such cases should be reviewed by a cytologist, colposcopist, and histopathologist at the colposcopy multidisciplinary team meeting (MDTM) before future management is decided. Information on the organisation and conduct of the MDTM can be found in relevant NHSCSP guidance.[12]

## 4.10 Cytological follow-up of women treated for CIN and ‘test of cure’

Women who have been treated for CIN should be returned to community-based recall, irrespective of their excision margin status. A cervical cytology sample should be taken six months after treatment.

- Where the cytology sample is reported as negative, borderline, or low-grade, a reflex HR-HPV test will be undertaken. Women who are positive for HR-HPV will be referred for colposcopy. Women who are negative for HR-HPV will be recalled for a repeat cytology sample in three years, irrespective of their age. The three-year repeat is managed according to standard HR-HPV triage protocols.
- Where the cytology sample is reported as high-grade dyskaryosis or worse, women must be referred for colposcopy. An HR-HPV test is not necessary.

If the test of cure cytology sample is performed in a hospital setting instead of in the community, it should be taken in a cytology clinic, as a formal colposcopic examination is not required.

### 4.11 Follow-up management of women treated for CGIN

All women treated for CGIN should undergo cytological follow-up. The first sample should be taken six months after treatment. If it is negative, then cytology should be repeated six months later (i.e. at 12 months after treatment) and then annually for the subsequent nine years (minimum standard).[12] Ideally, six-monthly samples would be taken for five years, followed by annual samples for a further five years (best practice).[12] All follow-up samples must contain endocervical cells.

### 4.12 Follow-up management of women referred to colposcopy as part of HR-HPV triage or test of cure

When women are referred to colposcopy as part of HR-HPV triage, and their colposcopic examination is satisfactory and normal, they should be returned to community-based routine recall. Subsequent samples will be taken at three- or five-yearly intervals, depending on their age.

When women are referred to colposcopy as part of test of cure, and their colposcopic examination is satisfactory and normal, their next sample will be taken in three years, irrespective of their age. If this subsequent sample is negative, the woman will return to routine recall (at three- or five-yearly intervals, depending on her age).

### 4.13 Use of HR-HPV testing outside of HPV triage and test of cure

The aim of HR-HPV testing is to identify those women who can be discharged from colposcopy to appropriate recall in the community. However, the use of HR-HPV testing outside of the HR-HPV triage and test of cure protocols may assist with the management of some clinical scenarios. To prevent the overuse of HR-HPV testing, it is recommended that all such cases are discussed at the colposcopy MDTM before an HR-HPV test is performed.

HR-HPV testing may be of use in the following clinical scenarios:

1. Women undergoing long term colposcopic surveillance for low-grade CIN or unresolved abnormal cytology, who have not previously been tested for HR-HPV. This could include women with cervical stenosis where colposcopy is non-contributory.
2. Women who experience difficulty tolerating colposcopy, whose examinations are therefore unsatisfactory.
3. Women with a persistent mismatch between high-grade cytology and low-grade histology, which has been discussed at the colposcopy MDTM, with the result that a decision not to treat has been reached.

Additionally, HR-HPV testing may be of use in the management of women who have undergone hysterectomy for CIN, or whose hysterectomy specimens have been found to contain CIN, who subsequently present with abnormal vault cytology but no evidence of high-grade VAIN. However, it should be noted that this use of HR-HPV testing falls outside of the NHSCSP.

A negative HR-HPV sample in the above scenarios may guide appropriate management, which may include discharge to appropriate recall or avoidance of clinical intervention.[13]

### 4.14 Women under cytological surveillance following a test taken before the implementation of HR-HPV triage and test of cure

Some women will be under cytological surveillance following a test taken before the implementation of HR-HPV triage and test of cure. Women will continue in cytological surveillance if the test was taken not more than five years previously, did not result in a referral to colposcopy, and was reported as 'borderline change' or 'mild dyskaryosis' using the older terminology from the earlier screening protocols outlined in the second edition of this publication, now superseded. These women may not be returned to routine recall following their first or second negative cytology result without a negative HPV test.

Either these women should be confirmed to be HR-HPV negative or at least three negative cytology tests (on samples taken at intervals at least six months apart) must be reported before the woman can be returned to routine recall.

# 5 HR-HPV TESTING

## 5.1 Management of low-grade cytological abnormality

Previous NHSCSP guidance recommended that women with persistent borderline change in squamous cells, and those presenting for the first time with low-grade dyskaryosis, should be referred for colposcopy. However there is accumulating evidence that triage of such women by HR-HPV testing is more sensitive, though slightly less specific, for detection of high-grade CIN.[14,15]

The results of the NHSCSP LBC/HPV pilot showed that HR-HPV triage decreased the number of repeat cytology tests and reduced the time taken to return women to routine recall, though it resulted in a large increase in the number of referrals to colposcopy. HR-HPV triage was found to be feasible and acceptable to women, while the results of an economic analysis concluded that it was also cost-effective, in terms of both quality of service provided and life-years saved.[16,17]

In 2007, the Sentinel Site study was launched, with the aim of providing information on the probable effects of implementing HR-HPV triage at a national level, with particular emphasis on rates of referral to colposcopy, and the positive predictive value (PPV) of this approach. Results suggested that the mean HR-HPV-positive rate was 53.7% in women with borderline change, and 83.9% in women with low-grade dyskaryosis. Across the six study sites, the data range for the percentage of women found to be HR-HPV positive per cytology finding lay between 34.8% and 73.3% for women whose cytology was reported as borderline, and between 73.4% and 91.6% for women whose cytology was reported as low grade. At the single site using both LBC technologies there was no difference in the detection rate between the two. The PPV of an HR-HPV test was 16.3% for CIN2 or worse, and 6.1% for CIN3 or worse.

The results of the study suggest that triaging women with borderline or low-grade cytological abnormalities using HR-HPV testing will allow approximately one-third of this group to be returned immediately to routine recall. Prompt referral for colposcopy will avoid the need for repeat cytology in the remainder, although it is acknowledged that variation in HR-HPV-positive rates will result in differing colposcopy workloads.[18] It has consequently been recommended that HR-HPV triage is implemented throughout the NHSCSP, and guidance on this process is now available.[7,19]

## 5.2 Follow-up after treatment for CIN

Previous NHSCSP guidance recommended that women who had been treated for low-grade histological abnormality (HR-HPV-associated changes or CIN1) had follow-up cytology at 6, 12, and 24 months after treatment. If all results were negative, these women could be returned to screening at the routine interval.[12] Women who had been treated for high-grade CIN (CIN2 or CIN3) required 6- and 12-month follow-up cytology, and annual cytology for the subsequent nine years, before returning to screening at the routine interval.[12]

However, there is accumulating evidence that HR-HPV testing provides a more sensitive, but slightly less specific, follow-up test than repeat cytology alone.[14,15,20] Results from the Sentinel Site study show that HR-HPV-negative women who have been previously treated for CIN have a very low risk of cervical neoplasia. ‘HPV test of cure’ therefore uses a woman’s HR-HPV status to assess her risk of having residual or recurrent disease following treatment for CIN.

Test of cure is carried out six months after treatment, and involves both cytology and HPV-testing. Women whose cytology samples are reported as high-grade dyskaryosis or worse are returned to colposcopy without undergoing an HPV test, and are followed up according to national guidelines.[12] All other women are managed according to their HR-HPV test result. Those who are HR-HPV negative are recalled in three years, and can revert to routine recall thereafter. Whereas formerly a minimum of 10 years of annual follow-up cytology was required, women can now return for just two or three cytology tests at the routine intervals (depending on their age) in the decade following treatment.[21] All women who are HR-HPV positive at test of cure are returned to colposcopy.

The implementation of HR-HPV testing for triage and test of cure is predicted to result in approximately 605 000 fewer cytology samples per annum in the NHSCSP.[7]

## 5.3 Follow-up after treatment for CGIN

All women treated for CGIN should undergo cytological follow-up. The first sample should be taken six months after treatment. If it is negative, then cytology should be repeated six months later, at 12 months after treatment, and then annually for the subsequent nine years (minimum standard).[12] Ideally, six-monthly samples would be taken for five years, followed by annual samples for a further five years (best practice).[12] All follow-up samples must contain endocervical cells.

## 5.4 Follow-up after treatment for invasive cervical cancer

Guidance on the follow-up of women after treatment for early-stage cervical cancer has been issued by the NHSCSP.[12]

## 5.5 Follow-up after treatment for SMILE

Follow-up after SMILE (stratified mucin-producing intraepithelial lesion) is by cytology. The first sample should be taken six months after treatment. If it is negative, then cytology should be repeated six months later, at 12 months after treatment, and then annually for the subsequent nine years (minimum standard). Ideally, six-monthly samples would be taken for five years, followed by annual samples for a further five years (best practice).

## 5.6 HR-HPV tests available for use in the NHSCSP

There are a number of HR-HPV tests available in the UK. The NHSCSP has performed a comparative analysis of the CE-marked tests to assess their suitability for use within the programme and their performance in relation to the accepted Qiagen Hybrid Capture 2 test. Details of those considered appropriate for use in the NHSCSP for HR-HPV triage and test of cure can be found at:

www.cspnhs.org.uk

# 6 CODES FOR STANDARD CYTOLOGY RESULTS, HR-HPV INFECTION, AND ACTION

## 6.1 Call and recall

The call and recall of women for cervical screening is managed by the National Health Applications and Infrastructure Services (NHAIS) system, formerly known as the Exeter System. Each time a woman is screened, standard details are captured on her cervical screening record, including:

- The coded cytology result.
- The HR-HPV infection code (as applicable).
- The action code, which indicates recall, or any other action required as a result of the test.

## 6.2 Standard coding schemes

The NHAIS system accepts only standard codes within national code sets for cytology results, infection status, and recommended actions. See Appendix 2 for a summary of these.

### *6.2.1 Cytology result codes*

Cytology result codes follow the national coding scheme, as described in Chapter 3. Where a laboratory uses a detailed clinical coding scheme for test results, the information must be translated to the appropriate national code for transmission to the NHAIS system.

Additional codes are used for results that are subject to HR-HPV testing, in accordance with the standard protocol for HR-HPV triage and test of cure. These codes are alphabetic, to distinguish them from standard result codes:

G Corresponding to numeric code 0 (?glandular neoplasia (non-cervical)).
N Corresponding to numeric code 2 (negative).
M Corresponding to numeric code 3 (low-grade dyskaryosis).
B Corresponding to numeric code 8 (borderline change in squamous cells).
E Corresponding to numeric code 9 (borderline change in endocervical cells).

The NHAIS system validates every cytology result coded G, N, M, B, or E to ensure that a valid HR-HPV infection code is associated with it.

### *6.2.2 HR-HPV infection codes*

The results of HR-HPV testing are recorded using a standard infection code as follows:

0 No HR-HPV DNA detected (i.e. negative).
9 HR-HPV DNA detected (i.e. positive).
U HR-HPV test result unavailable or unreliable.

The 'U' infection code indicates that no accurate HR-HPV test result could be obtained from the sample. It should be used in the following circumstances:

- The HR-HPV test failed and could not be repeated using the same sample, so the HPV result is unavailable.
- A cytology sample, which would have been reported as inadequate due to poor cellularity but for the presence of borderline features, is HR-HPV tested and the result is negative. Where it is unconfirmed by an internal control, this HPV result is unreliable.
- A cytology sample, which would have been reported as inadequate but for the presence of borderline or low-grade features, cannot be HR-HPV tested because of its poor cellularity, so the HPV result is unavailable.
- A cytology sample requires an HR-HPV test, but there is insufficient fluid for testing, so the HPV result is unavailable.
- A cytology sample has been pre-treated with a substance that precludes the HR-HPV test, so the HPV result is unavailable.

Under no circumstances should the 'U' infection code be used in cases in which an HR-HPV test cannot be carried out due to equipment failure or any other problem unrelated to the quality of the sample.

### *6.2.3 Reporting of incidental infections*

The reporting of infections is not part of the screening programme. However, laboratories may, by local agreement, report any incidental infections that can be reliably identified in cervical samples. Infection reports should be returned to the woman's GP or sample-taker for individual management. Laboratories should not send codes relating to incidental infections to the NHAIS system for inclusion in a woman's cervical screening record.

### *6.2.4 Action codes and recommendations for management*

The action code instructs the NHAIS system to recall a woman for future cytology tests at an appropriate interval.

- Action code 'A' is used for routine recall at the standard age-appropriate interval. This action code also indicates that a woman can be ceased from the recall system when her next routine test would fall after her 65th birthday.
- Action code 'R' is used where a further test is recommended at a specified interval (which must not be greater than the routine recall interval). Action code 'R' must be accompanied by an integer suffix to indicate the interval, in months, for the recall.
- Action code 'S' is used to suspend a woman from recall pending the outcome of a colposcopy referral. If no subsequent updates are made to the woman's screening record, she will be re-invited for further tests no more than 12 months after the date of the colposcopy referral. This is a failsafe measure to ensure that no-one is suspended from recall indefinitely.
- Action code 'H' indicates that no action is required, i.e. that no changes should be made to the woman's recall date. It is commonly used to record the results of non-NHS tests on the NHAIS screening record without affecting the woman's NHS recall date. It may be used only with the result categories 'inadequate' or 'negative'.

Laboratories *must* assign an action code to each test result, prescribing the actions to be followed. Administrative staff *must not* determine or modify action codes without the express permission of the reporting laboratory.

The NHAIS system will validate all action codes to ensure that they are appropriate. In particular, the system will validate routine recall recommendations in light of a woman's screening history, and reject these if further surveillance is indicated, e.g. after test of cure. The NHAIS system will also validate early repeat recommendations to ensure that the specified recall interval is not excessive for the circumstances.

The standard national action codes cannot be adapted for local use. This will ensure consistency of interpretation and use across the country and should improve the effectiveness of failsafe procedures, especially where women move from one laboratory or geographical area to another between screening events.

Clinical and administrative staff may wish to refer to the guidelines for the call/recall system and the definitions of action codes on the NHAIS system at:

www.connectingforhealth.nhs.uk/systemsandservices/ssd/downloads/cervical/contents/index_html.

## 6.3 Coding multiple diagnoses

In rare cases, a woman's cytology test may reveal the co-existence of non-cervical glandular neoplasia with cervical abnormalities. Treatment of the former falls outside the scope of the screening programme; therefore it is the latter result that should be recorded and sent to NHAIS to determine the woman's management within the screening programme. This will ensure that the woman is subject to NHSCSP failsafe systems. See section 4.8 for the management of women requiring gynaecological referral.

## 6.4 Cytology result, HR-HPV infection, and action code combinations

Each of the three components of a test result may be recorded independently. However, code combinations must be valid in accordance with the HR-HPV triage and test of cure protocol. Appendix 2 gives details of the code combinations supported by the NHAIS system.

## 6.5 Audit

Regular multidisciplinary audit is required to ensure that the codes sent by the laboratory are interpreted correctly by the NHAIS system and lead to appropriate management.

# 7 CRITERIA FOR EVALUATING CERVICAL CYTOLOGY

## 7.1 Performance indicators – introduction

In recent years, organised cervical screening in England has reduced both the incidence of, and mortality from, cervical cancer.[22,23] The performance of the majority of cervical screening services in this country must have been satisfactory for this nationwide effect to have been achieved. Further, a number of observational studies have demonstrated the effectiveness of cervical screening using cytology, often by estimating its 'protective effect'.[24] However, while the programme's overall standards are acceptable, remarkable geographical variations in performance have occurred, both between neighbouring health regions[25] and between laboratories.[26]

Unlike modern screening programmes, cytological cervical screening has never been subjected to randomised controlled trials. Setting performance indicators for the programme is difficult in these circumstances, because there is no 'gold standard' against which performance can be compared. Furthermore, as the programme does not track screening history using a cohort approach (unlike the breast and bowel cancer screening programmes), many basic measures cannot be evaluated directly, e.g. the CIN2 detection rate or the recall rate.

Efforts to set new performance measures must therefore concentrate on identifying outliers in the data and subjecting them to scrutiny. This should ensure a more even service across the country and will identify those laboratories where further investigation may be required. The amended performance criteria must also take account of recent changes to the national programme, including the use of LBC and the implementation of HR-HPV triage.

## 7.2 Philosophical issues

The philosophical issues surrounding cervical screening are particularly complex, due to a number of interrelated factors: the nature of cervical screening; the population of women being screened; and clinical preferences with regard to the trade-off between sensitivity and specificity.

Firstly, the cervical screening programme aims to detect pre-invasive disease (CIN1, CIN2, and CIN3), but there is no universal agreement as to the priority given to each degree of abnormality. Is it desirable to have 100% sensitivity for CIN3 alone? Or should the programme give equal priority to the detection of both CIN2 and CIN3, or even to all three grades of CIN? Secondly, considerable variation exists in the level of background disease incidence in the eligible population. Thirdly, individual clinicians have different preferences as to whether the programme should focus on 'first doing no harm' or on detecting all disease, irrespective of its probability of becoming invasive. Detecting high rates of pre-invasive disease at CIN1 or less is considered to be undesirable by those in the former group, but those of the latter school believe that it is necessary to achieve the highest possible sensitivity for CIN2 or worse.

## 7.3 Assumptions behind the new performance measures

In any screening test, there is always a trade-off between sensitivity and specificity. As CIN2 and CIN3 are treatable and carry a much higher risk of developing into invasive disease than CIN1, this document assumes that a high sensitivity for CIN2 or worse is desirable. Such a judgement follows the general mission statement for the NHSCSP, which states that 'the objective of cervical screening is to reduce cervical cancer incidence and mortality by screening with a high sensitivity for the detection of CIN2 or worse, whilst maintaining a high specificity'.

The methods of measuring performance that are presented here aim to highlight outliers in datasets. They have been designed on the basis that laboratories with unusual results should be required either to justify their difference from the majority or to effect changes that will bring their performance in line with the majority. The aim is to ensure a more even service across the country.

This approach implies a practical balance between sensitivity and specificity. On the one hand, it is not desirable to have a high proportion of women referred to colposcopy who receive eventual outcomes of 'CIN1 only' or 'HPV changes only'. Such services will be deemed to be operating at too low a specificity. On the other, it is not desirable to have high numbers of screen-detected 1A cancers, when these cases could have been identified as CIN2 or CIN3. Services with high levels of 1A cancers will therefore be considered to be operating at too low a sensitivity for CIN2 and CIN3.

The purpose of the performance indicators is to provide measures that enable the programme to operate at an optimal ratio of maximum benefit to minimum harm. The benefit is the reduction in cervical cancer incidence and mortality, and the harm is overdiagnosis and overtreatment of lesions that are not destined to progress.

The following sections provide two types of laboratory performance criteria, with two different weightings. Firstly, there are mandatory performance measures, based on inadequate sample reports, positive predictive value (PPV), and referral value (RV). Secondly, there are optional performance measures, which should be followed by those laboratories aiming to exemplify good practice. These are based on the mean CIN score (MCS), a comparison of abnormal predictive value (APV) and PPV, and the HPV-positive rate for borderline/low-grade samples.

Although the performance indicators are routinely calculated from the laboratory KC61 returns, they refer to, and are influenced by, the whole service, which includes cytology, colposcopy, and histology. Most performance indicators (with the exception of those outlined in section 7.7) are designed to be calculated by the laboratories themselves, but the identification of outliers requires analysis of the annual KC61 returns, which are aggregated and reported centrally.

## 7.4 Criteria for investigation and difficulties with some previously used methods

Previous performance measures worked on the principle of investigating those laboratories with a performance that fell outside a set range (from the 10th to the 90th percentile) on four particular indicators. For instance, if a laboratory's percentage of high-grade (moderate) or worse sample reports was above or below set limits, performance standards were said not to have been met. However, the difficulty with this method is that it does not take into account variations in background incidence across the whole of the country. Consequently, laboratories in areas with high background incidence may feel pressure to reduce the percentage of high-grade (moderate) or worse samples reported, even though this could be detrimental. Conversely, those in areas with low background incidence could be encouraged to report samples as high-grade (moderate) or worse, without appropriate evidence.

Further, because investigation was mandated where laboratories lay outside the set range, it remained theoretically possible for 80% of laboratories to be flagged for further scrutiny. An examination of the data for one year revealed that 51% of laboratories required investigation, throwing into doubt the credibility and effectiveness of this methodology.

Two of the four measures that were previously used to assess performance have been retained as mandatory. These are the performance indicators governing inadequate results from cytology samples and the PPV. However, the criteria for investigation will be improved, and it is expected that this will reduce the number of laboratories requiring further investigation.

- In the case of inadequate sample reports, laboratories must be investigated by the relevant Quality Assurance team when their percentage of inadequate samples falls outside the 5th to the 95th percentile range for the data. Those laboratories falling below the 5th percentile may be reporting too few samples as inadequate, while those falling above the 95th percentile may be reporting too many as inadequate.
- Similarly, laboratories must be scrutinised when their PPV falls below the 5th percentile or above the 95th percentile range for the data. This should enable the PPV measure to identify those laboratories operating at a particularly extreme sensitivity/specificity trade-off.

These criteria are given in Table 2. *Failure to meet them must always trigger further investigation, leading to action where necessary.* The third criterion, the RV, is discussed in section 7.5.

**Table 2** New performance ranges

| Criterion | Performance indicator | Range |
|---|---|---|
| Inadequate sample reports | % all samples | 5th to 95th percentile |
| PPV for CIN2 or worse | % of women referred with high-grade cytology or worse, whose biopsy is reported as CIN2 or worse | 5th to 95th percentile |
| RV | Number of women referred to colposcopy to detect one CIN2 or worse lesion | 5th to 95th percentile |

## 7.5 Total predictive value (TPV) and referral value (RV)

The TPV is defined as the percentage of all women referred for colposcopy (excluding those referred with negative cytology samples or repeat inadequate samples) who have a histological outcome of CIN2 or worse. The denominator for the calculation is the number of women referred (action code 'S') with abnormal cytology (result code 3, 4, 5, 6, 7, 8, 9, M, B, E). The numerator for the calculation is the number of women with an outcome of CIN2 or worse.

The RV is the inverse of the TPV, and is defined as the number of women referred to colposcopy (excluding inadequate referrals) per detection of one CIN2 or worse lesion. The RV is a new mandatory performance measure.

Figure 1 shows that the median RV for 2010/11 was 2.22. The range between the 5th and 95th percentile was 1.72–3.70 women referred per CIN2 or worse lesion detected. Those laboratories falling outside this range should be investigated, e.g. the laboratory referring nearly five women for each CIN2 or worse lesion detected was possibly operating at too low a specificity.

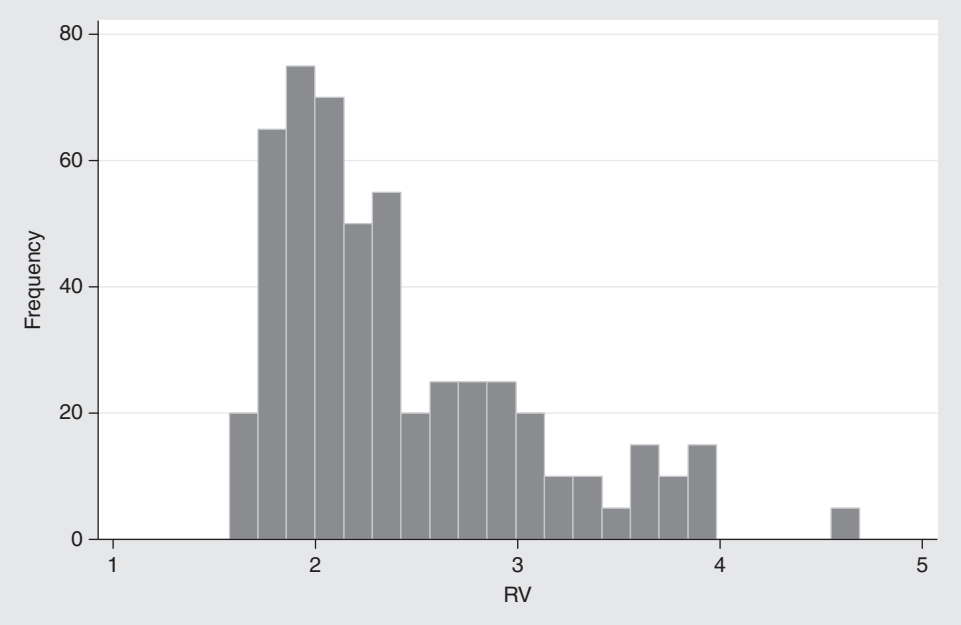


**Figure 1** RV from the 2010/11 KC61, part C2.

## 7.6 Mean CIN score (MCS)

The MCS is a simple method that has been developed to summarise the distribution of detected CIN cases as a single figure and is expected to vary between 1.5 and 2.5 (this may change as HR-HPV triage is introduced).[26] The MCS is based on all adequate cytology samples with adequate histology outcomes and is an optional performance measure.

Higher MCS values indicate that a greater proportion of the women referred to colposcopy were diagnosed with high-grade CIN. Lower values indicate that fewer women were diagnosed with high-grade CIN.

The advantages of the MCS method are: firstly, that it is robust to variations in background disease incidence (if the numbers for each laboratory are halved, the MCS is unchanged); and, secondly, that it is a very simple measure to calculate. However, no target limits are currently set, although laboratories with low or high values may be required to provide some justification for these observed distributions.

After the introduction of HR-HPV triage, the MCS will be calculated by taking data similar to that presented in Table 3 (for fictitious laboratories), and utilising this formula:

$$[(4 \times A) + (3 \times B) + (2 \times C) + D]/(A + B + C + D + E)$$

So, for example, the MCS score for Lab X is calculated thus:

$$[(4 \times 15) + (3 \times 50) + (2 \times 30) + 10]/(15 + 50 + 30 + 10 + 5) = 280/110 = 2.5.$$

**Table 3** Example of calculation of MCS for three laboratories (or services)

| Outcome of referral | Weighting | Column | Examples | | |
|---|---|---|---|---|---|
| | | | Lab X | Lab Y | Lab Z |
| Adenocarcinoma in situ/CGIN + cervical cancer stage 1A + cervical cancer stage 1B | 4 | A | 15 | 15 | 15 |
| CIN3 | 3 | B | 50 | 50 | 50 |
| CIN2 | 2 | C | 30 | 50 | 50 |
| CIN1 | 1 | D | 10 | 35 | 70 |
| HR-HPV only + no disease[a] | 0 | E | 5 | 15 | 65 |
| TOTAL | | | 110 | 165 | 250 |
| MCS | | | 2.5 | 2.1 | 1.5 |

a 'No disease' is defined as 'negative for HPV and no CIN or worse on colposcopic examination'. With HR-HPV triage the 'no disease' group will be limited (in theory) to those who were referred to colposcopy on the basis of a report of high-grade dyskaryosis, but who were subsequently found to have no disease.

The MCS can also be used to compare different levels of trade-off between sensitivity and specificity. Given that data from past years have shown that the number of CIN2 cases detected by a laboratory is usually the same or lower than the number of CIN3 lesions detected (even when the detection rates for CIN1, 'HPV only', and negative samples are high), the above table might create suspicions that Lab X is operating at too high a specificity to detect all CIN2 lesions, and therefore is highly sensitive only for CIN3. Lab Y's results suggest a high detection rate for CIN2 or worse, with a minimal number of referrals. Lab Z, however, is perhaps operating at too low a specificity, referring too many women for unnecessary colposcopy, indicated by the high number of cases receiving a diagnosis of 'CIN1' or 'HPV only'.

## 7.7 Positive predictive value (PPV) and abnormal predictive value (APV)

The PPV of samples reported as high-grade dyskaryosis (moderate) or worse for a histological diagnosis of CIN2 or worse is a standard performance measure. It should be reported alongside an additional measure, the APV, which calculates the percentage of samples reported as borderline or low grade that led to referral and subsequent histological diagnosis of CIN2 or worse. APV and PPV values are best viewed as a plot of APV against PPV, as illustrated in Figure 2, which shows data for the screening year 2010/11. The APV–PPV diagram is an optional performance measure.

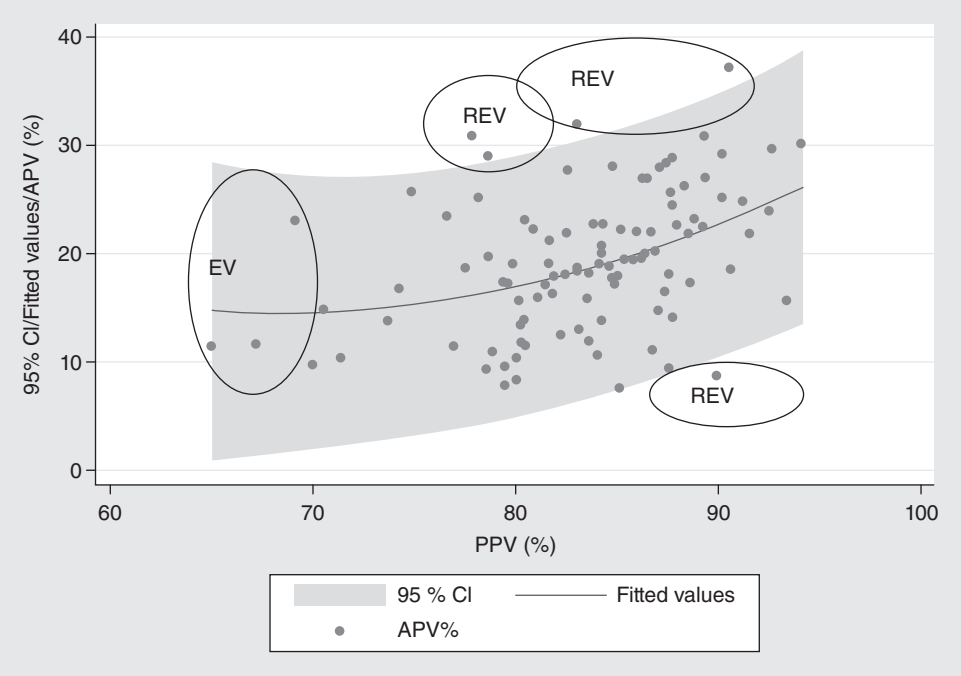


**Figure 2** APV–PPV diagram with laboratories selected for further study marked. Produced using STATA version 8 command: twoway (qfitci apv ppv, stdf) (scatter apv ppv), using data from 2010/11 KC61, part C2. 95% CI, 95% confidence interval; EV, extreme value; REV: residual extreme value.

The APV–PPV diagram allows the identification of various outliers.[27] Firstly, the diagram can be used to pinpoint laboratories with a true outlier value (TOV), for either APV or PPV. There are no examples of this in Figure 2, but if TOVs were present, they would be located away from the main distribution of results on the graph (i.e. well outside the grey area). Extreme values (EVs) indicate that laboratories may require further investigation. For example, a PPV for CIN2 of less than 70% may suggest a low level of specificity. Alternatively, residual extreme values (REVs) in which the APV value is unusual given the PPV, suggest a lack of correlation between cytology and histology, which should be examined further.

Following HR-HPV triage, we may expect the average APV to increase, as only those women with borderline or low-grade results who are HR-HPV positive will be referred to colposcopy.

Although the data are examined at the level of the laboratory, they draw on the performance of colposcopy clinics and histopathology laboratories. Both over-reporting and under-reporting by any of these should be considered when seeking explanations for outlying values. Potential confounding factors, such as an unusual mean age of women screened by the service, should also be borne in mind.

## 7.8 HR-HPV-positive rate for borderline/low-grade samples

A simple but useful measure, which complements the approach outlined in section 7.5, is to produce an analysis of variation in the HR-HPV-positive rate for borderline/low-grade cytology samples. This is an optional performance measure.

Laboratories with very low or very high proportions of HPV-positive borderline/low-grade samples (i.e. those falling above and below the 5th and 95th percentiles) should be subjected to further scrutiny. A very low HR-HPV-positive rate could indicate low test specificity; a high HR-HPV-positive rate may indicate too great a degree of specificity, corresponding to low sensitivity, such that disease may be being missed.

## 7.9 Rapid screening

Internal quality control is an essential component of laboratory Quality Assurance. With respect to primary screening, this is best achieved by the rapid preview or review of all negative and inadequate samples.

## 7.10 Audit of screening histories

Laboratories must comply with the requirements of the National Audit of Invasive Cervical Cancers. The aim of this audit is to understand why cervical cancers occur, despite the existence of an excellent screening programme, and to identify modifications to the programme that can reduce the incidence of, and mortality from, this disease.

The audit's remit extends across the whole screening process, but the review of cytological slides remains a central component. The purpose of this is educational: to review the previous management of the woman in cases in which invasive cancer has been detected; and to determine whether there are lessons that can be learnt for the benefit of the NHSCSP as a whole.

The collation of audit data is organised locally, by the Hospital-Based Programme Coordinator (HBPC), and regionally, by Quality Assurance Reference Centres. Detailed audit guidance has been set out in the NHSCSP document *Audit of Invasive Cervical Cancers.*[28] Updated guidance will be published in 2013 to standardise and update audit procedures in light of wider changes to the NHSCSP.

## 7.11 Information for sample-takers

The primary responsibility for ensuring quality of sample-taking rests with primary care commissioners. However, laboratories must support this process by analysing and making available data on inadequacy rates by practice.

## 7.12 Monitoring the outcome of women recommended for referral

Laboratories are responsible for ascertaining the outcome for all women they refer, including those women who refuse treatment or default from appointments. This may be achieved by correlating histology and colposcopy results, by communicating with GPs, local screening coordinators, and programme commissioners, and by sending failsafe reminder letters to GPs and sample-takers.

## 7.13 Liaison with cancer registries

Pathology laboratories must supply cancer registries with accurate data concerning invasive and microinvasive cervical cancers and CIN3/CGIN. It is therefore important that they are able to retrieve such cases from their computerised records.

# APPENDIX 1: BENIGN ENDOMETRIAL CELLS IN CERVICAL SAMPLES

The significance of cytologically benign endometrial cells in cervical samples varies with the phase of the menstrual cycle, and with the drug, clinical history, and age of the patient. However, in a population-based cervical screening programme, some, if not most, of the information listed above is often unavailable. This should be reflected in the clinical management advice provided.

There is now a considerable body of evidence suggesting that endometrial cells in a sample from a woman under the age of 40 do not indicate significant endometrial pathology. Therefore, normal endometrial cells found in a cervical sample from a woman of this age need not be reported.

In women over the age of 40, normal endometrial cells are significantly more likely to be found in the cervical sample up to the 12th day of the menstrual cycle than in the remainder of the cycle, and need not be specifically reported by the laboratory.

In women aged over 40, who are beyond the 12th day of the menstrual cycle, the finding of normal endometrial cells in a cervical sample may indicate endometrial pathology ranging from benign polyps to carcinoma. The association of normal endometrial cells in a cervical sample with significant pathology (endometrial hyperplasia and neoplasia) increases with age: it has been reported that endometrial carcinoma may be found in up to 13% of women over the age of 60 with normal endometrial cells in their sample.

However, normal endometrial cells found beyond the 12th day of the menstrual cycle in an individual over 40 may not indicate pathology if the woman is receiving oral contraceptives, hormone replacement therapy, or tamoxifen, or where an IUCD has been fitted. If this information is provided on the request form, an appropriate annotation/educational note should be made in the free text section of the report. Provided that there is no other clinical symptomatology to suggest endometrial disease, no further clinical action is required.

Normal endometrial cells identified in a sample from a woman aged 40 or over should always be reported if the menstrual, drug, and contraceptive history are not known (see above). They should also be reported where they are found in any postmenopausal woman, accompanied by a comment similar to the following: ‘Endometrial cells are present in a woman aged over 40. Such cells may be associated with endometrial pathology, particularly if out of phase or after the menopause. Referral for a gynaecological opinion should be considered in light of the menstrual, drug, and clinical history.’

If the day of the menstrual cycle is not known, and the sample is otherwise negative, then it should be reported as negative, with a comment similar to the following: ‘Endometrial cells are present but menstrual history not stated. If there is any history of abnormal vaginal bleeding, referral for a gynaecological opinion should be considered.’

# APPENDIX 2: NHAIS CYTOLOGY RESULT, HR-HPV INFECTION, AND ACTION CODES

## Cytology result codes

| Code without HR-HPV test | Code with HR-HPV test result[a] | Cytology result |
|---|---|---|
| 0 | G | ?Glandular neoplasia (non-cervical) |
| 1 | n/a | Inadequate |
| 2 | N | Negative |
| 3 | M | Low-grade dyskaryosis |
| 4 | 4 | High-grade dyskaryosis (severe) |
| 5 | 5 | High-grade dyskaryosis ?invasive squamous carcinoma |
| 6 | 6 | ?Glandular neoplasia of endocervical type |
| 7 | 7 | High-grade dyskaryosis (moderate) |
| 8 | B | Borderline change in squamous cells |
| 9 | E | Borderline change in endocervical cells |

a Note that cytology results of G, N, M, B and E *must* be accompanied by a valid HR-HPV result code.

## HR-HPV infection codes

| | |
|---|---|
| 0 | No HR-HPV DNA detected (i.e. negative) |
| 9 | HR-HPV DNA detected (i.e. positive) |
| U | HPV test result unavailable or unreliable |

Note that these infection codes may not be used with cytology results of 0, 1, 2, 3, 8, or 9.

## Action codes

| | |
|---|---|
| A | Routine recall at interval appropriate to age, or cease due to age (dependent on screening history) |
| R | Repeat at interval specified by laboratory. The interval should be given in months |
| S | Suspend due to referral |
| H | No action |

## Allowable cytology result/HR-HPV infection/action code combinations

| Cytology result | HR-HPV test result | | | |
|---|---|---|---|---|
| | None (no HPV test) | 0 (negative) | 9 (positive) | U (no result) |
| 0 | A, R, S, H | n/a | n/a | n/a |
| G | n/a | A, R, S, H | S | R, S |
| 1 | R, S, H | n/a | n/a | n/a |
| 2 | A, R, S, H | n/a | n/a | n/a |
| N | n/a | A, R, S, H | S | R, S |
| 3 | R*, S | n/a | n/a | n/a |
| M | n/a | A, R, S, H | S | R, S |
| 4 | S | S* | S* | S* |
| 5 | S | S* | S* | S* |
| 6 | S | S* | S* | S* |
| 7 | S | S* | S* | S* |
| 8 | R*, S | n/a | n/a | n/a |
| B | n/a | A, R, S, H | S | R, S |
| 9 | R*, S | n/a | n/a | n/a |
| E | n/a | A, R, S, H | S | R, S |

* indicates non-standard code combinations.
n/a, not applicable.

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