

NATIONAL CERVICAL SCREENING PROGRAMME

GUIDELINES FOR THE MANAGEMENT OF WOMEN WITH ABNORMAL CERVICAL SMEARS

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Forward

The Ministry of Health invited a working group to review the 1992 Abnormal Cervical Smears, National Consensus on a Protocol for Management,¹ after accepting the “Recommendations for Cervical Screening 1997”.² The Health Funding Authority has managed this project since April 1998. The group included gynaecologists, cytopathologists, an epidemiologist, a general practitioner and the national co-ordinator of the National Cervical Screening Programme (NCSP). Submissions were invited both before the initial meeting of the group and after circulation of the first draft of the proposed changes. The completed document has been reviewed by international authorities.

Previously published protocols have combined historically derived empirical information together with available evidence. Where possible, an evidence-based approach has been used in the preparation of this document. However because areas of uncertainty remain, the term **guideline** has been introduced in place of **protocol**, in recognition that the clinical context is also important.³ This change received almost universal support in the submissions received. Information from the National Cervical Screening Register, which has been in place since late 1991, was not adequate to assist the present working group. This must be available to assist future reviews.

The working party acknowledges the assistance and advice of those who made submissions, and the international authorities who reviewed the final document.

R W Jones

Chairperson of the working party

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Introduction

In the absence of prospective well controlled long term studies, indirect evidence has been taken into account in formulating these guidelines. The risk of invasive cervical or vaginal vault cancer is significantly higher in women who have been treated for high grade squamous intraepithelial lesions (HSIL) than in the general population.^{4,5} Those who develop invasive cancer after treatment, have rarely been treated for histologically proven low grade cervical intraepithelial neoplasia (CIN I).^{6,7} Nonetheless, women who have a low grade cytological abnormality have a small increased risk of developing cancer.⁸ More than half of low grade lesions regress spontaneously.^{9,10} There is evidence that cytological surveillance over 12-24 months with intervention only if the lesion persists or progresses, represents an appropriate balance between the disadvantages of unnecessary treatment and the very small risk involved in the conservative management of low grade lesions.^{11,12} This also appears to be more cost effective than immediate colposcopy.¹³ The three yearly screening frequency and monitoring of laboratory reporting through the New Zealand NCSP should enable the risk of invasive cancer from persistent, recurrent or new lesions to be minimised.

The introduction of the Bethesda System has created general uniformity in cytology reporting, but some variations in reporting practice between laboratories continue to create difficulties.¹⁴ The relevant professional bodies should make every effort to produce a national reporting style for cervical smears. Attention to quality assurance issues and continuing education are necessary in order to improve the standard of laboratory reporting in New Zealand.

The group sought to avoid unnecessary changes to the 1992 protocol . **The most important changes involve the management of low grade cytological abnormalities. For the purposes of management, atypical squamous cells of undetermined significance (ASCUS) and some**

categories of atypical glandular cells of undetermined significance (AGUS) have been included with low grade squamous intraepithelial lesions (LSIL - CIN1/HPV). Previously, women with a history of low grade abnormalities were required to have annual cervical or vaginal vault smears for life. Evidence to support this practice is lacking and it is now recommended that women in this group revert to 3-yearly screening after an appropriate interval.

Details of the management of the abnormal smear by the secondary caregiver (usually a colposcopist) are not included in this document. The group recognised that a minority of women presenting with certain smear abnormalities should ideally be referred directly to individuals with **special experience in colposcopic assessment and management.**

It needs emphasising that in most instances the cervical smear is a **screening test of asymptomatic women** with the object of detecting treatable pre-invasive squamous abnormalities of the cervix. Nonetheless, in spite of ideal screening and treatment, a small number of women will develop invasive cervical or vaginal vault cancer. Such cases should be rare and the **subject of a formal review process.**

Reporting Cervical Cytology

The Bethesda system has been adopted for reporting cervical smears in New Zealand. It is the responsibility of the smear taker to provide relevant clinical information, as outlined by the National Cervical Screening Programme request form. Each report indicates ADEQUACY of the specimen, a GENERAL CATEGORISATION as to whether the smear is within normal limits or not, and a DESCRIPTIVE DIAGNOSIS where appropriate. For the purposes of management, the term **abnormal smear** refers to all smears showing epithelial cell abnormalities, including atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGUS), but not including benign cellular changes. (i.e. infection and reactive epithelial cell changes.)

Summary of the Revised Bethesda System (1991) (TBS)¹⁵

Adequacy of the Specimen

- Satisfactory for evaluation
- Satisfactory for evaluation but limited by (specify reason)
- Unsatisfactory for evaluation (specify reason)

General Categorisation

- Within normal limits
- Benign cellular changes: See descriptive diagnosis
- Epithelial cell abnormality: See descriptive diagnosis.

Descriptive Diagnosis

Benign cellular changes

Infection

- Trichomonas vaginalis
- Fungal organisms morphologically consistent with Candida
- Predominance of coccobacilli consistent with shift in vaginal flora
- Bacteria morphologically consistent with Actinomyces
- Cellular changes associated with Herpes simplex virus
- Other

Reactive Epithelial Changes

Reactive cellular changes associated with:

- Inflammation (includes typical repair)
- Atrophy with inflammation (“atrophic vaginitis”)
- Radiation
- Intrauterine contraceptive device
- Other

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells of undetermined significance (ASCUS).

Qualify: favour reactive or favour premalignant/malignant process

NB. One specific sub-category of the ASCUS group is the small group “ASCUS, possible high grade lesion” which is accompanied by a recommendation for referral for colposcopy.

- Low grade squamous intraepithelial lesion (LSIL): encompassing CIN 1 and/or human papillomavirus (HPV)
- High grade squamous intraepithelial lesion (HSIL): encompassing moderate and severe dysplasia, CIN 2 and CIN 3/Carcinoma in situ (CIS)
- Squamous cell carcinoma

Glandular Cell

- Endometrial cells in a post menopausal woman who is not on hormone replacement therapy.
- Atypical glandular cells of undetermined significance (AGUS)
Qualify: favour reactive or favour premalignant/malignant process
- Endocervical adenocarcinoma in situ (AIS) *
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma.
- Extrauterine adenocarcinoma
- Adenocarcinoma, not otherwise specified.

Other Malignant Neoplasms: Specify

*NZ addition to TBS

ADEQUACY OF SMEAR

Satisfactory but limited smears

A smear may be adequate for evaluation, but limited for a variety of reasons. These include abundant neutrophils or blood obscuring 50-75% of the squamous cells present, poor fixation, scanty squamous cells, or the presence of cytolysis. The absence of an endocervical cell component is also included in this category. Although the quality of the smear is limited, enough clearly visible squamous cells are present for a report to be issued.

Recommendations for follow-up for satisfactory but limited smears (for all reasons except for the absence of an endocervical component) are that if the **smear result is normal**, the woman should have a smear in one year if she has a normal smear history. If there has been an **abnormal smear within the previous five years** (ASCUS, AGUS or worse) the next smear should be taken in six months. **If the smear result is abnormal**, follow-up will depend on the abnormality detected. Recommendations for follow-up of smears which lack an endocervical component, are discussed below.

Follow up for women who **repeatedly have smears that are satisfactory but limited by inflammation** (e.g. three or more consecutive smears) is controversial. There are no long term follow-up studies of women with repeated smears which are satisfactory but limited by inflammation as defined by Bethesda criteria. The group believes there is no justification for colposcopy or for smears to be taken more frequently than annually. Investigations should be directed at identifying a cause for the inflammation, including microbiological culture.

Cytolytic smears result from a proliferation of lactobacilli (normal vaginal flora). The action of these bacteria can cause a breakdown in squamous cell cytoplasm, making detection of abnormalities difficult. Cytolysis is most common in the latter part of the menstrual cycle. A smear taken around mid cycle usually resolves the problem, although a small number of women do have cytolytic smears repeatedly. The presence of cytolysis is not related to the technique of the smear taker in obtaining the smear.

An endocervical component includes endocervical columnar glandular cells and/or metaplastic squamous cells, and indicates that the transformation zone has been at least partly sampled. Smears without an endocervical component are reported as *satisfactory but limited* because the laboratory has no way of knowing if transformation zone sampling has occurred. An endocervical component may never be obtained in some women e.g. post menopausal women or women who have had previous surgery to the cervix.

The ultimate determination of specimen adequacy rests with the smearer, who must correlate the findings described in the cytopathology report, with clinical knowledge of the individual patient.¹⁵

The presence of an endocervical component in cervical smears is highly desirable, to demonstrate that the transformation zone has been sampled at least in part and to allow microscopic examination of glandular cells from the cervix. The proportion of smears containing an endocervical component also serves as an indicator of good smear-taking technique, and is an important parameter for quality assurance purposes for smear takers. However, there is no clear evidence that women whose smears lack an endocervical component are at greater risk of concurrent or subsequent abnormalities than women whose smears contain an endocervical component.^{16,17} If the smear taker

is satisfied that the cervix has been visualised and adequately sampled, and if the **smear result is normal while lacking an endocervical component**, there is no indication to repeat the smear earlier than the recommended screening interval. i.e. it is **recommended that the next smear is taken at the usual screening interval** of three years, if the woman has a normal smear history. This smear should be taken using a broom or both a spatula and cytobrush.

Unsatisfactory Smears

A cervical smear may be unsatisfactory for a variety of reasons. These include insufficient squamous epithelial cells, poor fixation, marked cytolysis or abundant neutrophils or blood obscuring more than 75% of the squamous cells present. The report will provide the reason why the sample is unsatisfactory. There is evidence to indicate that smears that are repeated at short time intervals, are less likely to detect significant lesions.¹⁸ The **recommendation for follow-up** is that unsatisfactory smears are repeated at 1-3 months, ideally around mid-cycle. Referral for colposcopy should be considered after three consecutive unsatisfactory smears.

DESCRIPTIVE DIAGNOSIS

Reactive Epithelial Changes (Inflammation/Repair)

Inflammation of the cervix is common, and some neutrophils are present in most cervical smears. When neutrophils are abundant, the squamous cell component may be obscured, resulting in satisfactory but limited smears, or unsatisfactory smears. Inflammatory cells may be associated with a specific infectious agent e.g Candida. The organisms may be apparent in the smear, but in many women, specific microbiological culture will be required to identify the microorganism responsible.¹⁹ The presence of inflammatory cells may or may not be associated with reactive epithelial cell changes. These reactive cells can usually be distinguished from dysplastic cells. If there is any doubt, the smear will be reported as showing atypia of undetermined significance, with a comment as to whether a reactive or neoplastic process is favoured. The term “inflammatory smear” should be avoided, because of the confusion as to whether the term refers to smears with abundant and obscuring neutrophils, or to smears showing reactive epithelial cell changes.

Recommendations for follow-up:

If the smear shows **reactive epithelial cell changes** the next smear should be obtained at the normal screening interval. Repeated satisfactory smears with reactive epithelial cell changes are not an indication to repeat the smear early, or to refer for colposcopy.

Some infections occasionally induce epithelial cell changes which can be difficult to distinguish from dysplasia, and in these cases, the laboratory may report the smear as showing atypical cells of undetermined significance and recommend another smear after treatment of the infection.

Atypical epithelial cells of undetermined significance:

Atypical squamous cells of undetermined significance (ASCUS)

This term encompasses a variety of squamous cellular changes which cannot be specifically classified. These changes exceed the features usually expected in benign reactive processes but are insufficient for a diagnosis of HPV or squamous intraepithelial lesion (SIL). In the Bethesda system the term “atypical” has this restricted meaning only. It should not be used in the context of benign change associated with reactive or repair processes, inflammation or infection. The laboratory will comment on whether a reactive lesion or SIL is favoured.

An ASCUS report identifies a patient who is at risk for SIL. However, these cytological abnormalities occur for a variety of reasons, and in many women the changes observed do not persist in subsequent smears. For women with a persisting abnormality, a significant number show SIL on colposcopic biopsy, which is usually low grade but may be high grade.²⁰ In a small number of smears, there are specific cell changes that are suspicious of high grade SIL, while not diagnostic (ASCUS - Possible HSIL). These smears should be specifically identified in the cytology report, with a recommendation for referral for colposcopy.

Atypical glandular cells of undetermined significance (AGUS).

This description applies to glandular cells which demonstrate changes which exceed those normally expected in benign reactive processes but which are insufficient for a diagnosis of AIS. It is usually possible to determine whether the atypical cells are endocervical or endometrial in origin. Smears showing “equivocal AIS” should be reported as AGUS, with features suggestive of AIS. The concept of a precursor lesion to AIS i.e. endocervical glandular dysplasia, is controversial. Its natural history is as yet uncertain and reproducible cellular changes for it are lacking.

In follow-up studies of patients who have “atypical endocervical cell” reports, squamous lesions are the commonest abnormalities detected on biopsy.²¹ Endocervical adenocarcinoma (in-situ or invasive) is found in a minority of cases.

Recommendations for follow-up are as follows (See flow chart):

For women with **ASCUS** results and a normal smear history, the next smear is taken at 6 months and if this smear is also abnormal, colposcopy is recommended to allow a definite diagnosis to be made. In the small number of cases in which the report specifically identifies the possibility of **HSIL**, direct referral for colposcopy after the initial smear, is recommended.

Follow-up for women with **AGUS** results and a normal smear history, depends on the further qualification as to whether a reactive or dysplastic lesion is favoured. Women with a report “**AGUS-favour reactive**” should another smear taken in 6 months, and if the second smear is also abnormal, colposcopy is recommended. Women with smears reported as **AGUS-favour dysplasia** should be referred for colposcopy after the initial smear, because of the recognized difficulties of sampling and diagnosis of glandular lesions.

Low grade squamous intraepithelial lesion (LSIL)

This category encompasses CIN 1 (mild dysplasia) and/or a definite diagnosis of HPV. As the cytological distinction between HPV alone and HPV with CIN 1 can be difficult, the smear may be reported as LSIL (CIN 1/HPV). It should be recognised that there is a subjective element involved in all of the triage modalities (cytology, histology and colposcopy) and these are most marked with low grade abnormalities.^{22,23,24} A proportion of smears reported as LSIL will have histologically proven high grade abnormalities.

Immediate colposcopy following a single LSIL smear result allows early histological diagnosis and avoids the possible risk of the patient defaulting. However, such a policy needs to be balanced by the high spontaneous regression rate of LSILs,^{9,10} the unnecessary anxiety caused in some women and the additional cost involved.

Recommendations for follow-up (see flow chart):

Women whose smears show **LSIL**, with no previous abnormality, should have the next smear taken at six months, and if this smear is also abnormal, then referral for colposcopy is recommended.¹²

Women whose smears show HPV only, are managed in the same way as women whose smears show CIN 1.

More than half of LSILs are reported to regress spontaneously.^{9,10} Following colposcopy and histological confirmation of LSIL, it may be appropriate in the first instance to manage by observation alone. This would require six-monthly smears and at least annual colposcopy. Treatment is indicated if there is persistence or progression. It should be stressed that while HPV-induced epithelial abnormalities (such as condyloma or CIN) can be treated, there is no method of treating subclinical or latent HPV infection in the genital tract.

The recommendation for long term follow-up for women who have had a histologically proven diagnosis of LSIL (HPV and/or CIN 1), has changed

While a small increased, long term risk of cervical cancer is still present after treatment for LSIL, the risk is not considered large enough to justify annual screening after three normal follow up smears. Annual smears for life after a diagnosis of LSIL are no longer recommended, and instead, a return to a 3-yearly screening interval is recommended, provided there have been 3 normal smears (at intervals in accordance with the flow chart) after the diagnosis and/or treatment of the low grade abnormality.^{8,11} After returning to 3-yearly screening, further abnormal smears are managed as a new episode of abnormality, with the proviso that colposcopy is recommended the first time a follow up smear demonstrates LSIL following **conservative** treatment for CIN.

High grade squamous intraepithelial lesion (HSIL)

This category encompasses CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia/carcinoma in situ).

Recommendations for follow-up (see flow chart)

All women whose smears indicate **HSIL** or raise the possibility of invasive carcinoma should be referred directly for colposcopy. If colposcopic examination of the cervix shows no sign of any abnormality, the whole genital tract should be reviewed. This should include careful clinical inspection and colposcopy of the entire lower genital tract and review of possible sites of origin for neoplastic cells in the upper genital tract.

The recommendation for **long term follow-up** after a histologically confirmed diagnosis of HSIL and treatment, is that annual smears should continue until age 70. If any further abnormal smears occur, the woman should be referred again for colposcopy.

Any woman with a history of high grade vulval or vaginal intraepithelial neoplasia (VIN,VAIN) should have annual cervical or vaginal vault smears until age 70.²⁵

High grade glandular lesions

Adenocarcinoma in situ (AIS)

The cellular changes characteristic of adenocarcinoma in situ (AIS) of the cervix are being increasingly recognised and should be reported whenever sufficient criteria are present.

Referral to an experienced colposcopist is recommended. Cytology follow up is as for HSIL (see flow chart).

Carcinoma

Women whose smears show squamous carcinoma, adenocarcinoma or any other malignant neoplasm should be referred immediately to an experienced colposcopist.

Long term follow up for women treated for invasive carcinoma should follow the recommendations of the gynaecological oncologist involved.

COLPOSCOPY

There appears to have been a general improvement both in the training and performance of colposcopy in New Zealand. However, much colposcopy is performed in relative isolation and without any review process. Studies have demonstrated considerable interobserver variability and variation in diagnostic accuracy among practising colposcopists, particularly with low grade abnormalities.²⁴ Examples of invasive carcinoma following colposcopically directed ablative therapy to the cervix continue to occur in New Zealand. Minimum standards and quality for those practising colposcopy in Britain have recently been outlined by the National Health Service Cervical Screening Programme in association with the British Association of Colposcopy and Cervical Pathology.²⁶ They recommend that in order to maintain skill levels, individual colposcopists need to manage a minimum of 100 new cases each year. This working group accepts this standard.

The group recognises that certain abnormalities create additional difficulties for the colposcopist and that individuals assessing such cases should demonstrate **additional experience**. In this document, an asterisk * is placed alongside certain cytology abnormalities (glandular abnormalities, cytological evidence of invasive carcinoma and HSIL in pregnancy). In these circumstances it is desirable for women to be examined by an **experienced colposcopist**. The group recommends that an experienced colposcopist should have a minimum of at least five years post Fellowship experience, manage at least 150 new colposcopy cases each year (and where appropriate, supervise at least 75 teaching cases each year) and be an active member of a multidisciplinary team involved in the ongoing audit of the cytology, colposcopy and histology of women presenting with abnormal smears.

Larger colposcopy units should allow time and provide facilities for the training of junior medical staff. Candidates for the Membership of the Royal Australasian College of Obstetrics and

Gynaecology are now required to pass an in-hospital clinical assessment of colposcopy and the treatment of cervical disease. In smaller centres one individual should be responsible for cases marked with an asterisk *. All colposcopists should regularly review the results of their assessment and treatment with their peers and cytopathologists. Accurate concise records should be maintained and relevant information relayed to pathologists and the National Cervical Screening Register.

The urgency of colposcopic examination depends on the degree of abnormality indicated by the smear or by clinical examination. For women in whom there is a clinical suspicion of invasive carcinoma, an immediate colposcopy/gynaecological oncology appointment should be sought. For women in whom the smear is suspicious of invasive disease, the opinion of an experienced colposcopist should be sought. These two groups of women should be seen within one week.

In women who have high grade smear abnormalities (CIN 2-3), colposcopy should be performed within one month. For women with persistent low grade abnormalities, as previously defined, colposcopy should be carried out within six months of referral.

Colposcopic examination during pregnancy can be difficult. Ideally this should be performed by an experienced* individual and as early in the pregnancy as possible.

Women who are oestrogen deficient may require 30-50 micrograms of ethinyloestradiol for 7-10 days prior to colposcopy. Local oestrogen may be appropriate in some circumstances. This regimen is also suitable immediately prior to subsequent smears where the laboratory has indicated oestrogen deficiency.

COLPOSCOPICALLY DIRECTED TREATMENT

Colposcopically directed treatment of CIN reduces the risk of invasive cervical cancer by 95% during the first eight years after treatment.⁴ A small diagnostic biopsy is taken at the initial

colposcopic assessment before definitive treatment is performed. The type of treatment offered will depend on local facilities and expertise. There may occasionally be a place for therapeutic excision (loop) biopsy at the initial colposcopic assessment (“see and treat”) depending on the particular clinical circumstances and the experience and expertise of the colposcopist involved. A proportion of cases of “see and treat” report normal histology. There is no case for “see and treat” when the referral smear shows minor abnormalities.^{27,28}

Women with HSILs should be treated within two months of histological confirmation.

Management of LSIL should be completed within six months of the decision to treat.

90% of women should be seen within the recommended intervals while awaiting colposcopy or treatment.

Treatment methods can be divided into two groups.

1. Ablative therapy in which the lesion is destroyed

This method requires thorough colposcopic examination and biopsy and that any suspicion of invasion is absolutely excluded. The disadvantage of ablative therapy is that tissue is not available for histological review. Ablative treatment may be by electrocoagulation, needle diathermy, cryocautery or laser, depending on local availability and expertise.

2. Excision biopsy

In general, these techniques are preferable because tissue is available for histological examination.

- a) Loop excision e.g. Large loop excision of the transformation zone (LLETZ)
- b) Laser conisation.

c) Cold knife cone biopsy. This is indicated where the whole lesion cannot be visualised or if there is a suspicion of invasive disease. Cone biopsy may be considered an option for the definitive treatment for women with early microinvasive disease (Stage 1A1).

3. Hysterectomy

This may be desirable for women with both a cervical abnormality and other gynaecological pathology. It may also be the best management for persistent or recurrent disease in women who have completed childbearing. Full colposcopic assessment prior to hysterectomy to define the extent of the cervical abnormality is essential if the lesion extends onto the cervical portio or the vagina. The hysterectomy should preferably be performed by the vaginal route.

Follow up after treatment

A colposcopy and cervical smear should be performed 4-6 months after treatment. Colposcopy enables the early diagnosis of treatment failures in the presence of false negative smears.²⁸ Further cytological follow up should follow the recommendations on the flow chart. Any woman who has ever had CIN 2/CIN3 or AIS and who subsequently has another abnormal cervical smear requires further colposcopy.

Women who have had a **total hysterectomy** and who at any time in the past have had histological evidence of a high grade lesion should be followed with annual vaginal vault smears until age 70 years. Those who have had histological evidence of CIN 1 should have 3-yearly vaginal vault cytology, until age 70 years.

Women who have had a total hysterectomy for a benign condition, with no histological evidence of cervical dysplasia or malignancy either previously or in the hysterectomy specimen, do not require vaginal vault cytology.²⁹

HPV DNA Typing. This is currently under investigation to determine its usefulness to confirm the presence of HPV, and to stratify women into lower and higher risk categories, particularly for women with LSIL or ASCUS/AGUS smears. The working group believes that while such tests may have potential benefits, the results of international studies already in progress should be awaited before this technology is adopted in New Zealand.

Immunosuppression increases the risk of a woman developing lower genital tract neoplasia (cervical, vaginal or vulval intraepithelial neoplasia or invasive disease).³⁰ In New Zealand, the most common cause of immunosuppression is the drugs used to suppress the immune system in certain medical conditions, e.g. renal transplants, systemic lupus erythematosus. Internationally, human immunodeficiency virus is of increasing importance as a risk factor in lower genital tract neoplasia. All immunosuppressed women who develop abnormalities should ideally be included in a long term programme of colposcopic surveillance, and should have annual smears.

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APPENDIX 1

SUMMARY OF THE “RECOMMENDATIONS FOR CERVICAL SCREENING 1997”²

1. Regular screening should commence at age 20 years, for women who have had sexual intercourse. Screening should be offered to all women who have ever had sexual intercourse, including lesbians.
2. The usual interval is 3 years for women with normal smear results. A further smear should be taken in one year if the woman has had no previous smears or if it is five or more years since the previous smear.
3. At age 70 years, women with normal smear results may cease to have cervical smears.
4. Women who have had a hysterectomy for a benign condition, with complete removal of histologically normal cervical epithelium, and who have no history of abnormal smears, do not need to continue to be screened.
5. Women with immunosuppression should have annual smears.
6. The cervical smear will be part of the investigation of women with signs and/or symptoms of cervical cancer. It is not sufficiently sensitive however, for a negative result to override clinical concerns. Such women should be referred for gynaecological assessment irrespective of the smear result.

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