

The new NHMRC guidelines for the management of abnormal Pap smears in asymptomatic Australian women

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Key Points

- **New Terminology system for Pap smear cytology (AMBS2004)**
- **Repeat Pap smear for most women with low grade squamous change**
- **Do not treat women with biopsy proven CIN1**
- **Refer all women with atypical glandular cell reports for colposcopy**
- **Use HPV testing as test of cure following treatment for CIN2 & CIN3**

In 2001 a multidisciplinary committee chaired by Professor Ian Hammond was convened to review the NHMRC (1994) guidelines for the management of asymptomatic women with screen detected abnormalities on a Pap smear. The Guideline Review Group (GRG) identified several key areas for consideration and a detailed literature review was commissioned in addition to two outcomes studies involving data collected by Australian Pap Test registries. It was recognized that there was new knowledge available regarding the natural history of HPV infection and the role of this agent in cervical carcinogenesis. The guideline development process is rigorously proscribed by the NHMRC and was carefully followed. This involved consultation with all relevant professional bodies and a wide range of clinicians and consumers. These guidelines are an evidence based population health package for Australian women in the context of the National Cervical Screening Program. The NHMRC council endorsed the new Guidelines on the 9th June 2005.

There are 6 major changes in the new guidelines and these are detailed below:-

Terminology: the Australian Modified Bethesda System 2004 (AMBS2004).

The need for new terminology arose from two concerns. First there was a need to move away from terminology that suggests an inevitable progression from CIN 1 through to CIN2 and 3 and to cancer. Such progression is now recognized to be a rare event. CIN 1 reflects an infective process and progression to more significant disease is related to persistent infection over many years. The second concern was to provide terminology that was compatible with other systems allowing international research data to be relevant to Australia. The new terminology relates to cytology (Table 1). The CIN terminology will be retained to describe histological diagnoses.

Repeat Pap smear for most women with low grade squamous abnormalities

The new terminology recognizes two categories of low grade squamous intraepithelial lesions (LSIL)

- Possible LSIL, previously known as non specific minor changes
- LSIL, previously know as CIN1 and HPV

These low grade reports are very common with approximately 100,000 each year in Australia. This arises because young Australian women (<25yrs) are screened and the two yearly screening interval in Australia results in the increased detection of transient abnormalities. Outcome data from Australian Pap test registries was used to underpin the final recommendations for the management of Australian women with these low grade abnormalities. These data and information from natural history studies on HPV infection support a delay in the timing of colposcopic assessment, to allow spontaneous resolution of the HPV infection. It is recommended that women with LSIL or possible LSIL should have a repeat Pap test in 12 months. Women who are over 30 years and who do not have the protection of a negative Pap test report in the preceding two to three years should be offered immediate colposcopy or a repeat test in 6 months.

The new low grade recommendations are safe for Australian women. The GRG constructed a model that estimated no extra cervical cancers would arise as a result of these recommendations and this view was endorsed by a meeting of independent Australian epidemiologists held in Nov 2004. A subsequent unpublished independent report (May 2005) from the National Centre for Epidemiology and Population Health at the Australian National University estimated there would be 50 fewer cancers resulting from the new guidelines, reflecting the inclusion of the possible LSIL group in the recommendation for colposcopy. It is probable that the number of women undergoing colposcopy for low grade abnormalities will increase.

Interestingly, there is no international consensus as to how women with low grade abnormalities should be managed. Due to the short 2 year screening interval in Australia, women with low grade abnormalities will be referred for colposcopy at the same time or earlier than women in other countries with an organized screening program (Table 2).

Do not treat women with biopsy proven CIN1 or HPV lesions

The previous guidelines were equivocal regarding treatment for biopsy proven low grade lesions. Evidence does not support treatment of these lesions which are likely to spontaneously resolve. The new guidelines recommend that treatment of biopsy proven CIN 1 and HPV should not be undertaken. Treatment is reserved for women who have or subsequently develop a high grade epithelial abnormality.

Refer all women with atypical glandular cells for colposcopy

In contrast to low grade squamous epithelial abnormalities, women who have atypical glandular cells of undetermined significance, or indeed any glandular cytologic abnormality, are recommended for colposcopic assessment by a colposcopist with expertise in the colposcopic evaluation of suspected malignancies or by a gynaecological oncologist. Colposcopic assessment of these lesions is notoriously difficult and there has been no impact on the incidence of glandular cancers of the cervix since screening has commenced. There are only 800 women with low grade glandular reports each year in Australia and the higher rate of invasive cancer diagnosis within 2 years of such a report justified this recommendation.

Use HPV & cytology as a test of cure for women treated for CIN 2 and 3

Women who test negative for high risk HPV subtypes following treatment for CIN 2 or 3 have a very low risk of further high grade cervical abnormality. Because the prevalence of HPV positivity falls quite sharply during the first year post treatment, it is recommended that HPV testing is introduced at 12 and 24 months (after treatment) in conjunction with cytology. Once a women has tested negative by both tests on two consecutive occasions then it is recommended that she return to the normal screening interval rather than annual cytology.

Do not report normal endometrial cells in post menopausal women

Laboratories currently report the presence of normal endometrial cells found in the Pap smear of women over the age of 45 years.. Reporting of this finding is no longer recommended *in asymptomatic women* because of the very low incidence of endometrial cancer (0.2%).

We anticipate that these new guidelines will inform gynaecologists and general practitioners in their care of women with screen detected abnormalities. We encourage all of our colleagues and trainees to read this document which details the evidence and recommendations for the optimal care of Australian women who have an abnormal cervical Pap smear. It is available at <http://www.nhmrc.gov.au/publications/synopses/wh39syn.htm>.

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Table 1. The Australian Modified Bethesda System 2004, comparison with previous terminology

New Australian NHMRC terminology AMBS 2004	Australian NHMRC endorsed terminology 1994	Incorporates
Squamous abnormalities		
Possible low-grade squamous intraepithelial lesion	Low-grade epithelial abnormality	Nonspecific minor squamous cell changes. Changes that suggest but fall short of HPV/CIN 1
Low-grade squamous intraepithelial lesion	Low-grade epithelial abnormality	HPV effect, CIN 1
Possible high-grade squamous lesion	Inconclusive, possible high-grade squamous abnormality	Changes that suggest, but fall short of, CIN 2, CIN 3, or SCC
High-grade squamous intraepithelial lesion	High-grade epithelial abnormality	CIN 2, CIN 3
Squamous cell carcinoma	High-grade epithelial abnormality	Squamous cell carcinoma.
Glandular abnormalities		
Atypical endocervical cells of undetermined significance	Low-grade epithelial abnormality	Nonspecific minor cell changes in endocervical cells.
Atypical glandular cells of undetermined significance	Low-grade epithelial abnormality	Nonspecific minor cell changes in glandular cells
Possible high-grade glandular lesion	Inconclusive, possible high-grade glandular abnormality	Changes that suggest, but fall short of, AIS or adenocarcinoma
Endocervical adenocarcinoma in situ	High-grade epithelial abnormality	Adenocarcinoma in situ
Adenocarcinoma	High-grade epithelial abnormality	Adenocarcinoma

Table 2. International comparison of suggested management of women with low grade squamous cytologic abnormalities and screening intervals.

Country	Screening Interval (years)	Cytology	Recommended Management
Finland	5	Pap 2 (atypical cells but no evidence of malignancy)	Not referred for further examination unless repeat cytology or other results are suggestive of malignancy.
Australia	2	Low-grade (possible LSIL and LSIL)	Repeat cytology in 12 months.
Canada	3	ASCUS & LSIL	Repeat cytology in 6 months.
New Zealand	3	ASCUS & LSIL	Repeat cytology in 6 months.
Netherlands	5	Pap 2 & 3a1 & 3a2	Repeat cytology in 6 months.
France	3	ASC-US LSIL	Repeat cytology <u>or</u> colposcopy <u>or</u> HPV testing. Repeat cytology at 4-6/12 months <u>or</u> colposcopy.
USA	3*	ASC-US LSIL	Repeat cytology <u>or</u> colposcopy <u>or</u> HPV testing. Colposcopy
UK	3 & 5	Borderline change Mild dyskaryosis	Colposcopy after 3 tests. Ideally colposcopy but repeat cytology acceptable.

* Over 30 years of age and after 3 negative tests