

*Screening to prevent cervical cancer: Guidelines for the management of asymptomatic women with screen-detected abnormalities*

Approved by NHMRC - 9 June 2005  
Implementation date - 3 July 2006

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**National Cervical  
Screening Program**

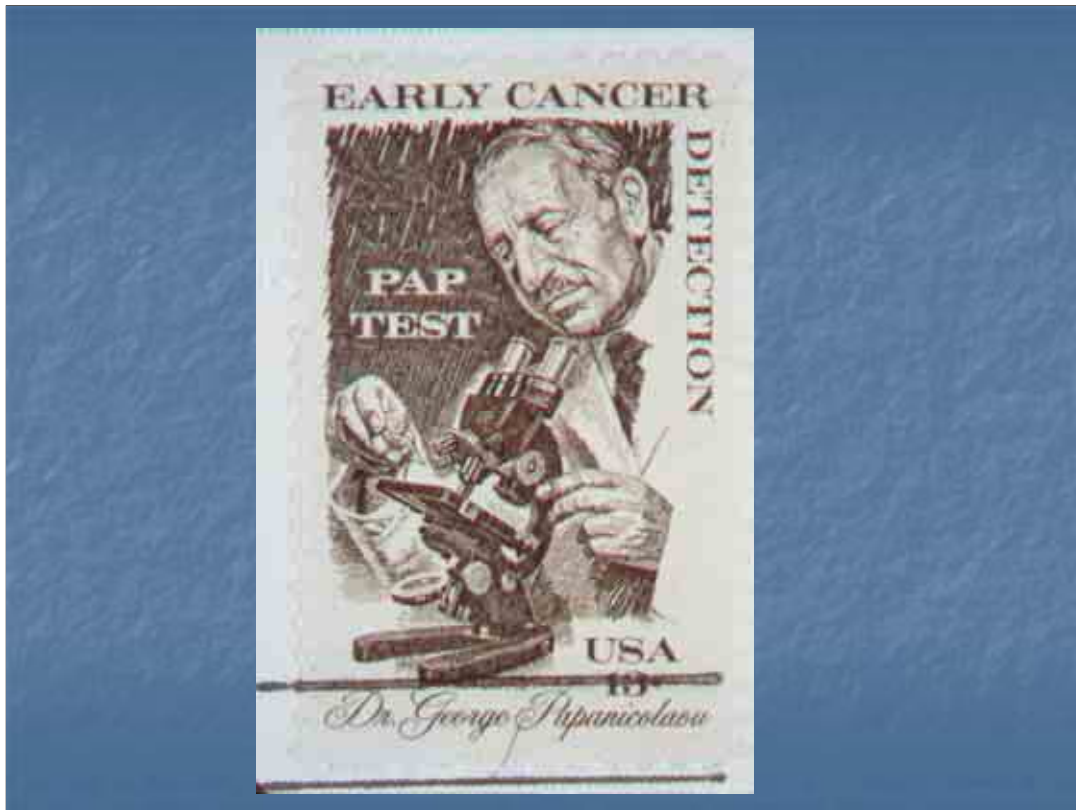
A joint Australian, State and Territory Government Initiative

Welcome to this presentation on the guidelines for the management of asymptomatic women with screen-detected abnormalities. In this presentation I will outline the major changes due to be implemented from 3 July 2006. It should be emphasised at the start that the guidelines are for **asymptomatic** women. Women with symptoms such as bleeding or discharge should be investigated regardless of their Pap smear results. Endorsement of these guidelines is for a period not exceeding five years (ie the next revision will need to have been approved by NHMRC before June 2010)

# Map of presentation

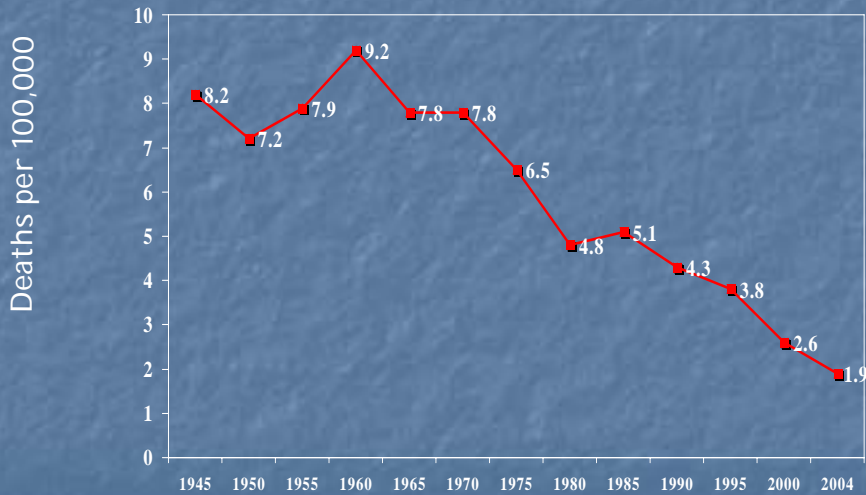
- Background on screening & summary of key changes
- New terminology
- Management of low grade abnormalities
- HPV – new knowledge
- Glandular abnormalities
- Normal endometrial cells
- Post treatment of biopsy proven high grade abnormalities
- Special clinical circumstances
- Safety of the new guidelines





Cervical screening was introduced opportunistically into Australia in the 1960s, but it was not until the advent of the “Organized Approach” program, launched in 1991, that we had a National Policy for when to start, when to stop and how often to screen women.

## Cervical Cancer Mortality Australia 1945 - 2004



■ Rates are age-standardised to the 2001 Australian population.

Source: AIHW General Record of Incidence of Mortality (GRIM Books).

Australia has an excellent screening program. This graph shows the decrease in mortality rates from squamous cell cancer falling from 7.7 deaths per one hundred thousand women in the early 1960s, to 1.7 per one hundred thousand women in the late 1990s and in 2004. Cervical cancer is now the 18<sup>th</sup> most common cause of cancer mortality in women in Australia (AIHW Cervical Screening in Australia 2002-2003).

# International Comparisons

	Mortality	Incidence
New Zealand	3.2	10.0
UK	3.1	8.3
Sweden	3.1	8.2
Canada	2.5	7.7
USA	2.3	7.7
Finland	1.8	4.3
Australia	1.7	6.9

From [www.dep-iarc.fr/GLOBOCAN](http://www.dep-iarc.fr/GLOBOCAN) 2002

On an international basis we vie with Finland for the lowest rates of incidence and mortality.



In 1994, as part of the “Organised Approach” the NHMRC published Guidelines for the Management of Women with Screen-Detected Abnormalities. NHMRC recommends that guidelines are updated every five years. The 1994 guidelines were rescinded and therefore we have had no official guidelines since 2000.

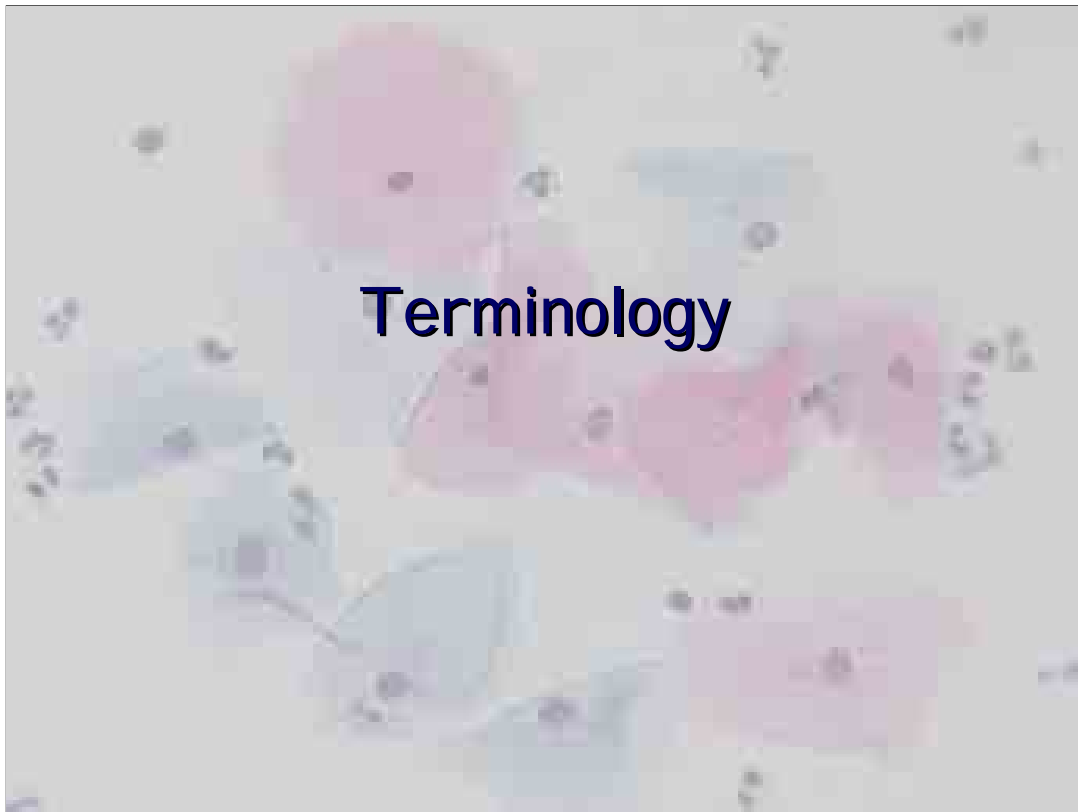
# Why change?

- Previous guidelines rescinded by NHMRC
- New knowledge about HPV
- Terminology not internationally consistent
- Unnecessary investigation & treatment
- Unnecessary anxiety about cancer
- Costs of treatment (physical, fertility, emotional, psychosexual, financial)

So, why do we need to change? Firstly, the previous 1994 guidelines were rescinded in 2001: we have worked under no official guidelines since then. Secondly, since the publication of the 1994 guidelines we have amassed an enormous amount of knowledge concerning the human papilloma virus and the role it plays in the development of cervical abnormalities. This new knowledge informs the crucial changes that we will be discussing. Thirdly, it was appreciated that the terminology we were using on Pap smear reports was neither nationally nor internationally consistent. This made our research difficult to compare with that from overseas. And, lastly, the Guidelines Review Group (GRG) considered that we have probably been responsible in our cervical screening program for much unnecessary investigation and treatment; unnecessary anxiety about cancer; and costs---physical, emotional, psychosexual and financial---without balanced gains.

# The six key areas of change

- New terminology system for Pap smear cytology
- Repeat a Pap smear for most women with low grade squamous change
- Do not treat women with biopsy proven CIN 1
- Refer all women with atypical glandular cell reports for colposcopy
- Use HPV testing as test of cure following treatment for high grade abnormalities (CIN 2 & 3)
- Do not report normal endometrial cells in post menopausal women.



Let's consider each of the major changes one by one.

1994 Terminology	New Terminology – AMBS 2004
Negative	Negative
Unsatisfactory	Unsatisfactory
Low-grade abnormalities <ul style="list-style-type: none"> <li>- Non-specific minor change</li> <li>- HPV effect</li> <li>- CIN 1</li> <li>- Glandular changes</li> </ul>	Squamous abnormalities <ul style="list-style-type: none"> <li>- Possible low-grade</li> <li>- Low-grade</li> <li>- Possible high-grade</li> <li>- High-grade</li> </ul>
Inconclusive	
High-grade abnormalities <ul style="list-style-type: none"> <li>- CIN 2, CIN 3, AIS</li> <li>- Cancer</li> </ul>	Glandular abnormalities <ul style="list-style-type: none"> <li>- atypical,</li> <li>- possible high grade</li> <li>- glandular,</li> <li>- high grade glandular</li> </ul>

The 1994 terminology categorised Pap smear reports by degree of abnormality (low-grade vs high-grade).

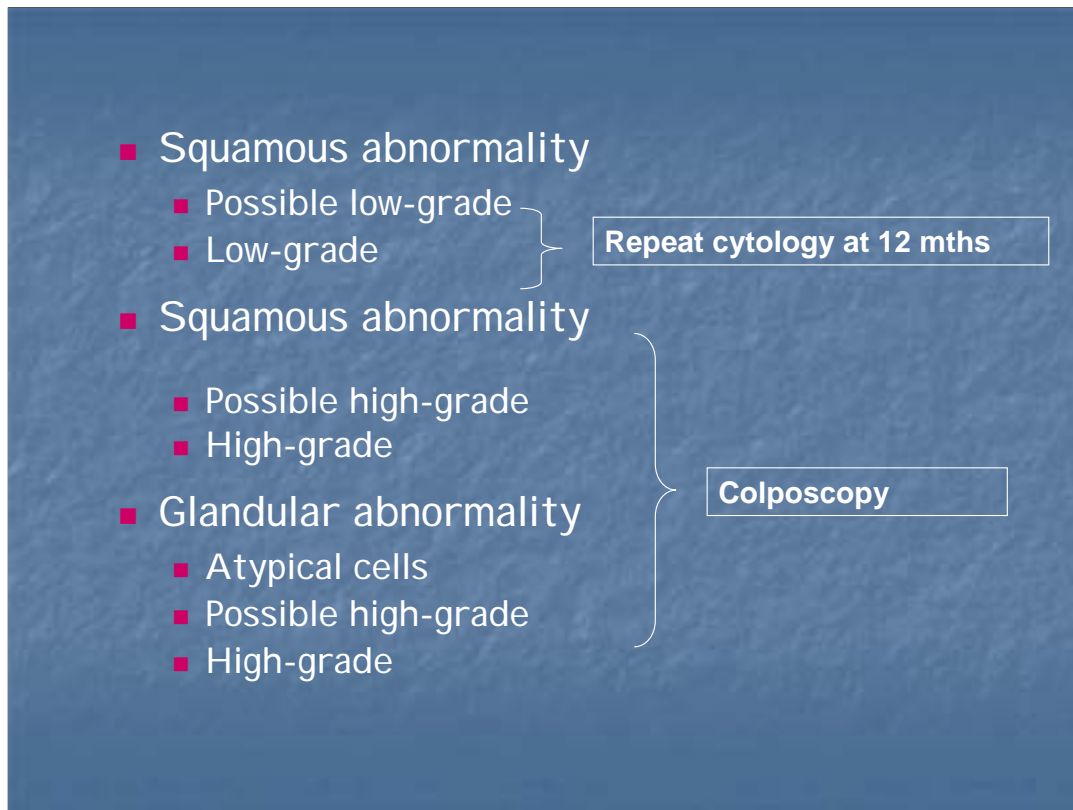
The new terminology (Australian Modified Bethesda System 2004 or AMBS 2004) uses the type of abnormality (squamous vs glandular) as the main categorisation.

While the new terminology combines CIN2 and CIN3 into one category, laboratories are still free to retain the distinction in their data collections.

Terminology for the reporting of histopathology remains unaltered. Note that the inconclusive category has been removed. Most of these reports will now probably be absorbed into the “possible high-grade” reports.

Initial management of abnormal smears is now simplified into two main streams.

The effect of this new categorization will be to simplify the initial management of abnormal Pap smears into two main streams.

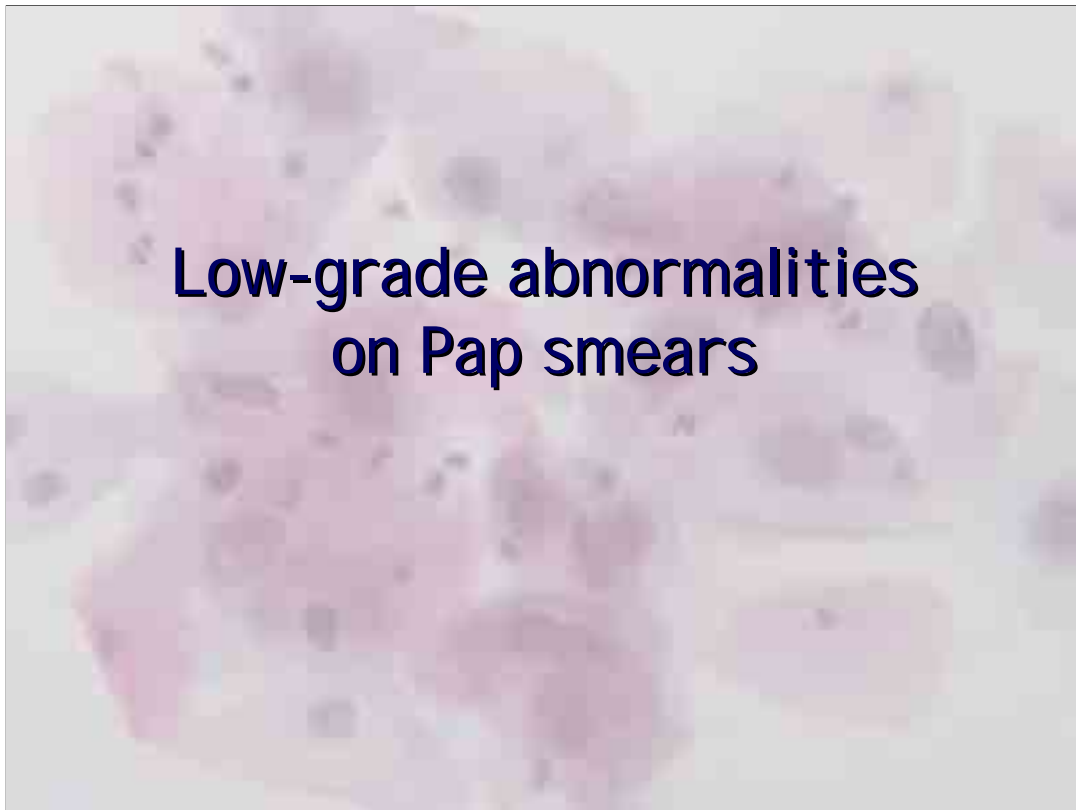


A low-grade abnormality will essentially have an initial recommendation of repeating the test at 12 months. A high-grade, or *any* glandular abnormality should be referred for colposcopy. Mixed abnormalities (ie both squamous and glandular) are managed on the basis of the glandular abnormality ie with colposcopy.

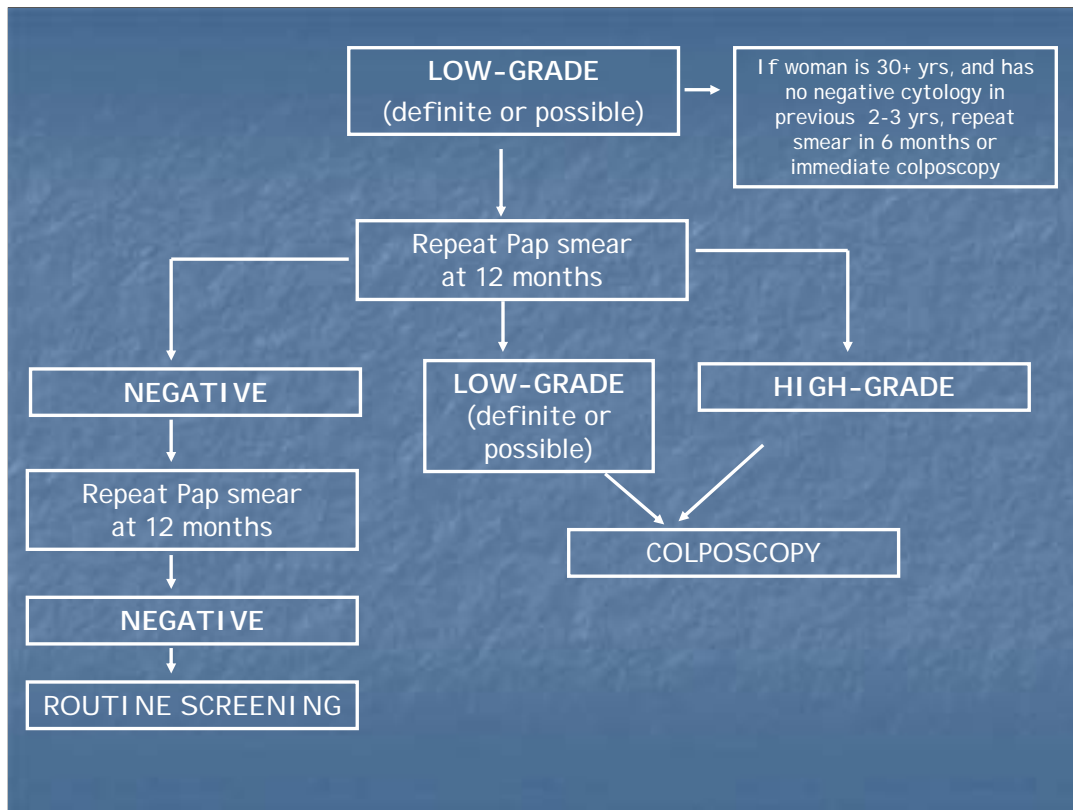
## Recommendations

- Negative
- 2 years
- LSIL/possible LSIL
- 12 months
- HSIL/ possible HSIL & glandular changes
- Colposcopy
- Unsatisfactory
- Repeat 6-12 weeks

In effect this will mean that you will be repeating most negative tests in two years; those with initial low-grade, or possible low-grade, reports (LSIL is low-grade squamous intra-epithelial lesion) will have another test in 12 months; and those with HSIL or possible HSIL (high-grade squamous intra-epithelial lesions) changes or any glandular changes should be referred for colposcopy. An unsatisfactory smear should be repeated in 6-12 weeks. Note that it is very important NOT to repeat a smear earlier than this. Doing so can result in a false negative smear.



Let's now consider in more detail the rationale behind the new recommendations for the management of low-grade abnormalities on Pap smears.



This flow chart illustrates the course of action for a woman whose initial Pap smear test is reported as being low-grade. Basically the test should be repeated at 12 months. If it still shows low-grade changes or if it's now reported as a high-grade, she should be referred for colposcopy. On the other hand, if it's negative, she can have a repeat in a further 12 months, and if this is negative, she can go back to routine two yearly screening.

There is one addendum: shown in the pink box. The reason for this recommendation is it is more likely that an "older" woman may have a persistent HPV infection and a slightly higher risk of a significant occult high-grade abnormality, even though the Pap smear suggests a low-grade change. Women over 30 years of age who have had regular normal Pap smears can be reassured they do not have a persistent HPV infection, so it is quite safe for them to have a repeat smear in 12 months. For those who have not had the reassurance of negative cytology in the past two to three years, it is safer to have an early repeat smear or a colposcopy.

The average duration between HSIL and cancer is between 10 and 15 years (Van Oortmarssen and Habbema 1991, Bos et al 1997 in *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities*, 3.5.1).

This means that even if the true state of a woman's cervix with a LSIL report is CIN 2 or CIN 3, she should still be a long way from cancer – say 10 years.

	Approx. no of women p.a
High-grade cytology	20,000
Low-grade cytology	100,000

Currently prevent about 1200 cancers per year

Still 400 invasive squamous cancers per year in women aged 20-69 yrs, almost all of whom lack a regular screening history

In Australia about 20 thousand women each year receive a report of a high-grade (or possible high grade) change; in contrast five times that number, that is 100 thousand, receive a low-grade report. Keep in mind that in Australia it is estimated that we currently prevent about 1200 cases of cervical cancer each year. Of the 400 that are diagnosed, 85% of these women have either not had a Pap smear in the prior 10 years, or have been under-screened. Seventy-five per cent of these women are over the age of 50.

	Approx. no of women p.a
High-grade cytology	20,000
Low-grade cytology	100,000

- Most of the **benefit** comes from treating women with **high-grade** cytology
- Most of the **harm** comes from investigating and treating women with **low-grade** cytology

Most of the benefit of the screening program comes from treating women with high-grade cytology; and most of the harm comes from investigating and treating women with low-grade cytology.

The low grade changes are due to HPV infection and nearly all will go away without any intervention.

A microscopic image showing several cells with pink and blue staining. The cells are irregular in shape and some show signs of abnormality, consistent with HPV infection. The text "New knowledge - HPV" is overlaid in the center.

## New knowledge - HPV

## New knowledge

- HPV
- Prevalence
- Time to regress
- Low-grade cytology mostly represents HPV infection of squamous cells

Let's then look more closely at the rationale behind these new recommendations for low-grade Pap smear reports. Since the previous guidelines were published in 1994 we have gained an immense amount of knowledge about the human papilloma virus and the role that it plays in the development of Pap smear abnormalities and cervical cancer. We understand much more about its prevalence; the time it takes for infection to regress, and its contribution to cellular changes on a Pap smear. Indeed, we know, for example, that low-grade cytology mostly represents HPV infection of squamous cells.

# Human papilloma virus (HPV)

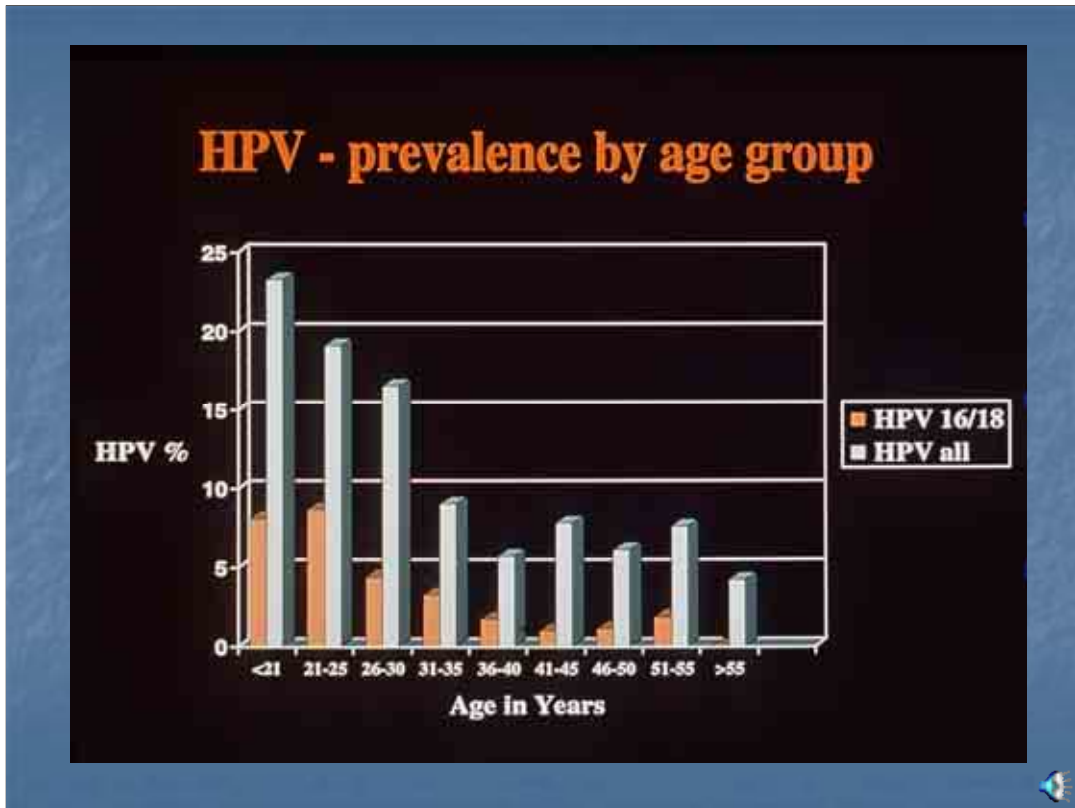
- Over 100 types of HPV
  - Species specific
  - Site specific
  - Multi-focal infection within a particular site
- Approximately 30 types infect genital region

There are over 100 different types of human papilloma virus. The types are designated according to DNA sequence. This virus is not only species specific, but it is also site specific. That is, it is not impossible, but it is very uncommon to find types that usually cause warts on the hand on the feet; or types from the feet on the genitals. However, within a particular site, the infection tends to be multi-focal. So, for example, if a woman has virus at the fourchette she will usually have it in the vagina and on the cervix. If a man has virus on the shaft of the penis, it will commonly be found on the scrotum. This is one of the reasons why it is so difficult to prevent the spread of HPV, even by using condoms. There are over 30 types of HPV that infect the genital area.

# Spread

- Almost always sexually transmitted
- Rarely: maternal to foetus transmission

Genital HPV types are spread through genital skin-to-skin contact. The virus gets in to the surface epithelium via micro-abrasions in the skin. Once in the epithelium it infects the nuclei of the basal cells. Vertical transmission, can occur but is very rare.



HPV is a common infection. Exact prevalence rates of HPV in Australia are unknown, but in the USA it has been estimated that around 75% of the adult population has some evidence of being, or having been, infected with genital types of HPV. Universally, the highest rates are found in young people between the ages of 18-28. In fact, in the first 10 years of sexual activity point prevalence rates approach 25%, and the lifetime risk of acquisition may be as high as 80%. Overall the prevalence in the sexually active population is thought to be around 20% depending on age.

# Prevalence

- Point prevalence in the first 10 years of sexual activity = 20-25%
- Lifetime prevalence = 80+%
- After the age of 30, prevalence drops to <5%

Infection with one or more of the genital HPV types is extremely common. If we were to take one hundred sexually active 18 year olds and look for evidence of genital HPV infection (this might be by examining for genital warts; looking for cellular evidence of HPV on a Pap smear or by doing HPV DNA tests) it could be anticipated that between 20 to 25 of them would have infection. This is a very high point prevalence. If we were to then test that same cohort yearly over the next 10 years, we would expect that the prevalence would rise to 80% or higher. However, most infection in young people is completely transient. After the age of 30, the prevalence drops to under 5%. Infection in this age group is much more significant because it is more likely to represent **persistent** infection - and that is what we're really interested in when it comes to the relationship between HPV and cervical cancer.

## “Low- Risk” HPV DNA Types

- Include types 6, 11
- Less frequent types include 26, 42, 43, 44, 53, 54, 55, 62, 66
- Mostly spontaneous regression over 1-2 years

Genital HPV types have been classified as being either “low” or “high” risk according to their association with high-grade lesions and cervical cancer.

Of particular significance are types 6 & 11, for reasons that we will discuss. Other low risk types include the ones listed. Infection with low risk types of HPV usually regresses over 1-2 years

## “Low-risk” HPV infection causes:

- Genital warts (mostly HPV 6 & 11)
- Low-grade squamous epithelial lesions (LSIL) on a Pap smear

HPV types 6 and 11 are responsible for around 90% of genital warts. These are benign (albeit unsightly) lesions that do NOT cause cervical cancer. Acute infection with HPV can result in nuclear changes that are consistent with the criteria for a low-grade change on a Pap smear.

## “High-Risk” HPV DNA Types

- Mainly types 16 and 18
- Less frequent types 31, 33, 35, 52, 58, 67 and 45, 59, 39, 68.

Of the “high-risk” types, 16 and 18 are the most significant as these two types are most frequently found in high-grade lesions and cervical cancer.

## “High-risk” HPV infection can cause:

- Cancers (mostly HPV 16 & 18)
  - Squamous and adenocarcinomas
    - HPV-18 associated with adenocarcinomas
  - Other anogenital cancers
    - Anal (85%); vulval; vaginal; penile (50%)

HPV 16 and 18 have been classified by the WHO as oncogenic viruses. WHO describes HPV infection as a “necessary but insufficient cause of cervical cancer”. More than 99.7 % of cervical cancers are positive for HPV DNA. Other contributing factors include smoking and possibly hormonal status as well as host cell factors, nutrition and other STIs. HPV types 16 and 18 are said to be responsible for about 70% of the world’s international burden of cervical cancer. These types are also found in a high proportion of low grade squamous changes but most of these infections will resolve spontaneously. HPV 18 is also associated with adenocarcinoma.

## New knowledge\*

- HPV infection: median clearance time 8 to 14 mths
- Most low-grade lesions regress quite quickly
  - Mean time **10.5 months**
  - **78% regression** at 12 months (95% CI 70-85%)
- Progression from low-grade to high-grade lesion is infrequent and slow
  - Mean time **86.4 months**

\*Schlecht et al, JNCI ,2003

Since 1994 our knowledge concerning HPV and cervical abnormalities has increased exponentially. We know that low-grade abnormalities are extremely frequent – most are not detected because of their transient nature. The median clearance time for a cervical HPV infection is between 8-14 months. In fact most low-grade lesions regress quite quickly: a mean time of 10.5 months. Close to 80% of low-grade lesions have resolved at 12 months. Even if a low-grade lesion does progress to high-grade (and this is infrequent), it will usually take around seven years to do so.

## New knowledge (cont'd)

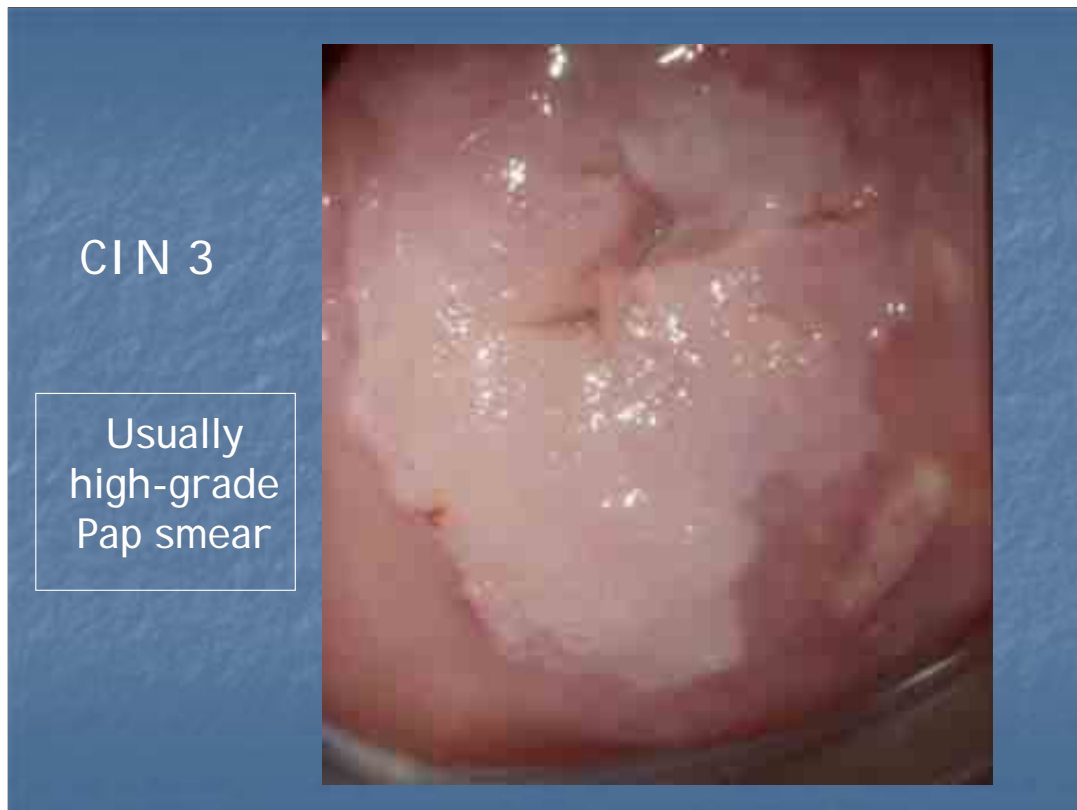
- Invasion usually occurs after years of persistence and expansion of CIN 3
- Typically a large amount of CIN 3 is present if a woman has microinvasive cancer
- When cytology is reported as low-grade and biopsy shows CIN 3, the amount of CIN 3 is usually very, very small

We also now understand that not all high-grade lesions progress to cancer. In fact, only around 20% of such lesions would actually progress to cervical cancer if left untreated, and any such invasion usually occurs after years of persistence and expansion of CIN 3 at the cervix. When a Pap smear is reported as low-grade but an occult high-grade is actually present, the amount of CIN 3 present is usually very, very small.

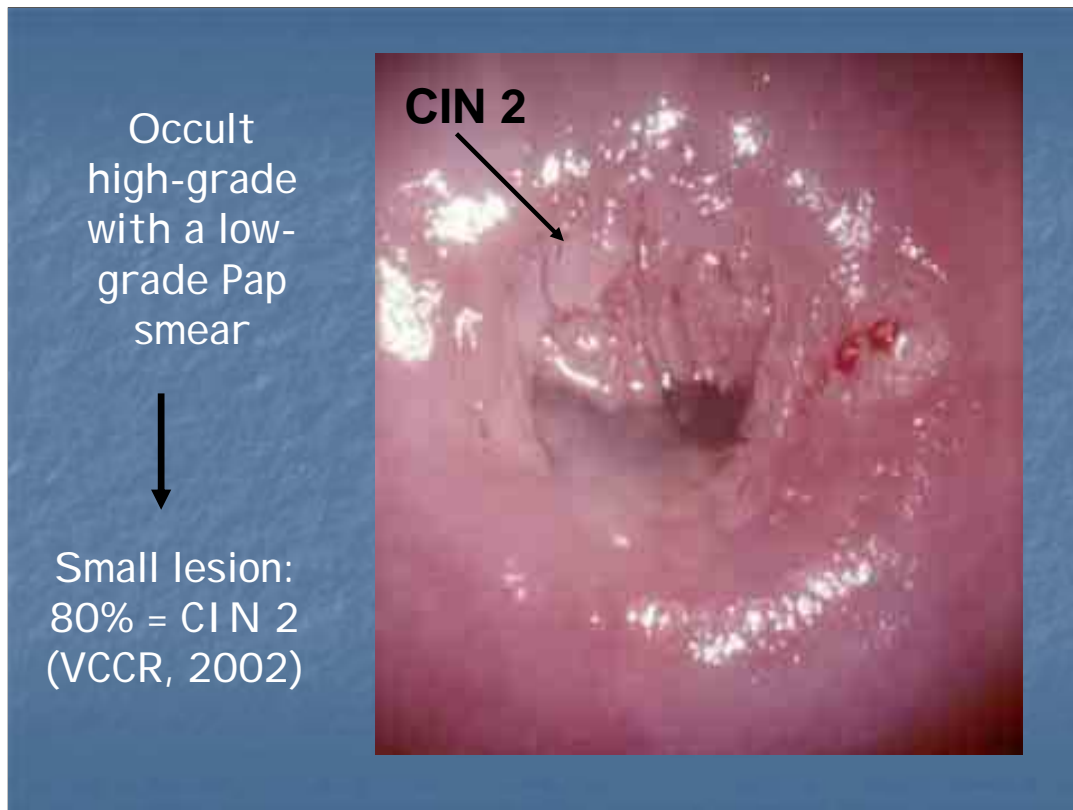
Cytology	Histology	Mean size of CIN 3 lesion
CIN 1	CIN 3	0.6 mm
CIN 2	CIN 3	5.3 mm
CIN 3	CIN 3	9.5 mm
-	Microcarcinoma & CIN 3	63.5 mm

Tidbury, 1992

This slide shows the results from a UK study (Tidbury, 1992) Women had a Pap smear reported as either CIN 1, 2, or 3. On biopsy all were shown to actually have CIN 3. i.e. CIN 3 was missed on the Pap smear of those women reported as having either CIN 1 or 2. But the interesting and significant point is that the amount of CIN 3 present increases dramatically as the Pap smear becomes more accurate. Not all CIN 3 is the same. When CIN 3 was confirmed in those women who had such a result indicated on Pap smear, the amount present was over 10 times greater (9.5 versus 0.6mm) than in those who had an occult CIN 3 reported as CIN 1. Moreover, there was usually 100 times as much CIN 3 present if the woman had microcarcinoma.



This colposcopic picture shows an area of CIN 3 confirming a high-grade Pap smear result. When the Pap smear is high grade we usually find a large obvious lesion and as you can see the area of aceto-white epithelium is considerably larger.



In contrast, this picture shows the cervix of a woman who has had a Pap smear indicating a low-grade lesion. On colposcopy she has been found to have a CIN 2 (the pale white area indicated by the arrow.) Note that this is a small area and that 80% of such lesions were found to be CIN 2 (rather than 3) using data from the Victorian Cervical Cancer Registry in 2002.

## Fluctuating abnormalities

Consider colposcopy if a woman has two low-grade or possible low-grade Pap smears (at least 12 months apart) within a 3 year timeframe, regardless of intervening normal cytology.

There will be occasions when management is not “black and white”. If a woman has fluctuating abnormalities, for example, if she has two low-grade or possible low-grade smears at least 12 months apart within a three year timeframe (regardless of intervening normal tests), then it is quite reasonable to consider colposcopy, and for the health professional to make this type of clinical decision.

## Example

- Feb 04      Low-grade cytology
- Feb 05      Negative cytology
- Oct 05      Possible low-grade cytology

→ Consider colposcopy

This is an example of such a woman. Here she has had a low-grade report in February 2003; negative cytology the following year; possible low-grade eight months later. In this instance it would be reasonable to refer her for colposcopy or to consider this as a possible re-infection with HPV after a previous clearance and decide to wait for a further cytological report in 12 months.

## Biopsy proven low-grade lesions

- Do not require treatment
- Rather, repeat Pap smear at 12 and 24 mths
  - If these two Pap smears are negative, return to normal screening
  - If either Pap smear shows low-grade change, repeat annually until at least two negative smears, then return to normal screening
  - If repeat Pap smear shows high-grade change, colposcopy

Having considered the management of low-grade lesions reported on a Pap smear, let's now turn to the new recommendation following a biopsy-proven low-grade lesion. Under the previous guidelines, recommendation varied according to the type of low-grade determined by biopsy: HPV was observed; CIN 1 was given the option of treatment or observation. The revised guidelines state that biopsy-proven low-grade lesions do not require treatment, because these lesions will nearly always resolve spontaneously. Instead, the recommendation will be to repeat the smear at 12 and 24 months. If these two Pap smears are negative, the woman can return to normal screening. If either Pap smear shows low-grade change, repeat annually until at least two negative smears, then return to normal screening. And if any repeat Pap smear shows high-grade change, refer for colposcopy.

## In summary, the low-grade recommendations

- Will result in more colposcopies but fewer treated women
- Colposcopies will be
  - targeted to women who are more likely to have cancer diagnosed in near future (older, under-screened women)
  - focused on women with persisting abnormal cytology
  - more evenly spread across spectrum of low-grade cytology
- The number of cancers occurring after low-grade cytology will be the same or less

In summary, it is very likely that the new low-grade recommendations will result in more colposcopies but fewer treated women. In particular, colposcopies will be targeted to women who are more likely to have cancer diagnosed in the near future (such as older and under-screened women), will be focused on women with *persisting* abnormal cytology, and will be more evenly spread across spectrum of low-grade cytology. It is estimated that the number of cancers occurring after low-grade cytology will be the same or less.



The fourth major change to be implemented with the revised guidelines is in the management of glandular abnormalities on a Pap smear.

- Very rare - about 1 in 1500 women have a Pap smear report of glandular abnormality (cf 75 squamous abns.)
- Important because adenocarcinoma now represents about 20% of all cases of cervical cancer in Australia

Glandular abnormalities (that is changes that have occurred to the columnar mucus-producing cells in the cervical canal) are rare. About 1 in 1500 women who have a Pap smear will have a report of a glandular abnormality compared to 1 in 75 who will have a squamous abnormality. However, they are important because adenocarcinoma now represents about 20% of all cases of cervical cancer in Australia, and while incidence of squamous cancer has been falling steadily, little impact has been made on incidence of adenocarcinoma.

Refer all women with  
atypical glandular cells for  
colposcopy

Colposcopy for glandular abnormalities should be performed by a gynaecologist with expertise in suspected malignancies or by a gynaecological oncologist.

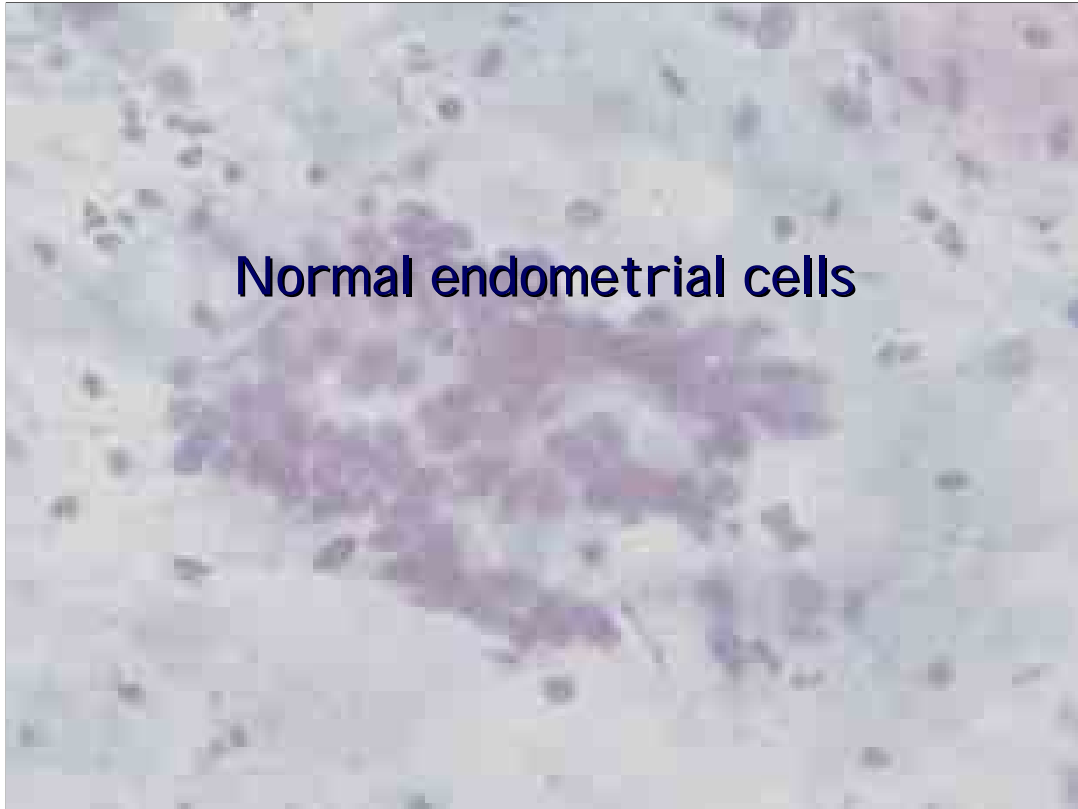
The revised guidelines recommend that colposcopy should be performed for **all** glandular abnormalities detected on a Pap smear, and that, wherever possible, this examination should be carried out by a gynaecologist with expertise in suspected malignancies, or by a gynaecological oncologist.

## Rationale for glandular changes

- Low-grade glandular abnormalities do not exist (acute HPV infection doesn't affect glandular cells in the same way as squamous cells)
- Neither cytology nor colposcopy are anatomically well-suited to detecting glandular disease
- Rate of cancer diagnosis within 2 yrs of a glandular abnormality on cytology suggests more intensive investigation is appropriate

The rationale behind this new recommendation includes these three facts:

1. low-grade glandular abnormalities do not exist (acute HPV infection does not affect glandular cells in the same way as it does squamous cells)
2. Because the columnar cells may be high in the canal, or deep within the epithelium, neither cytology nor colposcopy are well-suited to detecting glandular disease. This is why it is recommended that an expert in colposcopic evaluation undertake these examinations.
3. The rate of cancer diagnoses seen within two years of a glandular abnormality detected on cytology suggests that we should be more intensive in our investigation of these reports



The fifth major change is to the reporting of normal endometrial cells.

Normal endometrial cells in the Pap smears of asymptomatic postmenopausal women **should not be reported**.

(Symptomatic postmenopausal women require investigation, irrespective of their Pap smear status).

The revised guidelines recommend that normal endometrial cells in the Pap smears of asymptomatic post-menopausal women should **not** be reported. Of course, symptomatic postmenopausal women will require investigation irrespective of their Pap smear status.

## Rationale for not reporting normal endometrial cells

- Very low incidence of endometrial carcinoma (0.2%)
- The presence of normal endometrial cells in asymptomatic women does not indicate underlying cancer.

Previously, the reporting of normal endometrial cells in asymptomatic post-menopausal women has caused many dilemmas with practitioners uncertain about the necessity of referring these women for further investigation.

We now know that there is a very low incidence of endometrial carcinoma (0.2%), and the presence of normal endometrial cells in post menopausal women does not indicate underlying cancer. This is the rationale for **not** reporting their presence.

Normal endometrial cells do not require any further investigation in the asymptomatic woman. Once again, it must be emphasised that symptomatic women should continue to be investigated whatever their Pap smear result.



## Post-treatment of biopsy proven high-grade squamous abnormalities

(CIN 2, CIN 3)

The sixth and last major change that will be introduced is in the management of women after treatment of a high-grade squamous abnormality. Under the previous policy women who had a high-grade abnormality confirmed at biopsy were required to have annual Pap smears for life because treated women continue to be at a slightly higher risk of cervical cancer than women who have never had an abnormality. But we now appreciate that most women who are treated are fully cured and this new approach aims to separate out a much smaller group of women who retain the higher risk. These are women who have PERSISTENT HPV infection of the cervix with a high risk type of HPV.

We are able to do this by using a test for the “high-risk” types of HPV; this test is known as a HPV DNA hybrid capture test. You can do this test by taking a brush sample (rather like the cytobrush used for a Pap smear) after a Pap smear. The brush is inserted into the endocervical canal and rotated 360 degrees. You then break the brush into a small plastic tube (both of which your laboratory should be able to provide). Alternatively, if you are doing liquid-based cytology you can order an HPV hybrid-capture test on this.

Time since treatment	Pap smear	Colposcopy	HPV typing
4-6 mths	✓	✓	
12 mths	✓		✓
24 mths	✓		✓

- HPV typing has been added to the MBS for this clinical use only ('test of cure')

The guidelines recommend that 4-6 months after treatment for a high-grade lesion the woman should return to her gynaecologist for a repeat Pap smear and colposcopy. Twelve months after treatment she can see her regular practitioner for a Pap smear and an HPV test. Essentially, she continues to have both tests done at 12-monthly intervals until she has two sets of tests 12 months apart (a total of four tests) which are negative. HPV testing has been added to the Medicare Benefits Schedule for this clinical use i.e. "test of cure" after a high-grade lesion.

Time since treatment	Pap smear	Colposcopy	HPV typing
4-6 mths	✓	✓	
12 mths	Negative		Negative
24 mths	Negative		Negative

→ Return to 2 year screening interval when Pap smear and HPV typing are negative on two consecutive occasions

As illustrated in this slide, once two sets of tests (Pap smear and HPV test) are negative on two consecutive 12-monthly occasions, the woman can return to the usual two yearly screening program. If the follow-up Pap smear shows a high grade change then the patient should be referred for colposcopy. If the Pap smear shows only low grade change or the HPV test is positive, then the tests should be repeated each year - there is no need to refer back to the gynaecologist for colposcopy.

## Rationale for post-treatment changes

- Cervical cancer develops in the presence of **persistent** HPV infection
- A negative HPV test very accurately predicts the absence of HPV
- Allows large number of low-risk women (n ≈ 250,000) with treated abnormalities to return to the usual screening interval

Why can this now be recommend? Well, we know that cervical cancer develops in the presence of **persistent** HPV infection and that a negative HPV DNA test very accurately predicts the absence of HPV.

This change will now allow a large number of women (in the order of 250,000) who have been treated to return to the usual screening interval and stop smears at the age of 70.



There are certain special circumstances where the recommendations will differ from those of the mainstream.

These special clinical circumstances include:

- Pregnancy
- Immunosuppressed women
- Women exposed in utero to diethylstilboestrol

These special circumstances include pregnancy, immunosuppressed women and women exposed in utero to diethylstilboestrol (DES).

# Pregnancy

1. Follow the same guidelines as for the non-pregnant woman
2. Colposcopy is safe but may be more difficult, so an experienced colposcopist is recommended
3. Biopsy is usually not performed unless invasive cancer cannot be excluded.

Cervical cancer in pregnancy is not common, occurring in about 0.05% of pregnancies. The investigation of screen-detected abnormalities during pregnancy should follow the same guidelines as for the non-pregnant woman. In general, women who present with a low-grade abnormality should have a repeat test in 12 months. Women with high-grade lesions should be referred for colposcopy. Colposcopy during pregnancy is safe, but interpretation may be more difficult and, wherever possible, the examination should be done by an experienced colposcopist. Biopsy is usually not performed if the examiner is certain they have excluded invasive cancer.

# Immunosuppressed women

- Defined as:
  - CD4 count of < 400 in HIV-positive women
  - Transplantation with immunosuppressive therapy > 3 years
- On screen detected abnormality, even low grade, refer to colposcopy.
- Annual and indefinite follow up.

For the purposes of this recommendation immunosuppression is defined as:

- a). CD4 count of < 400 in HIV-positive women
- b) Transplantation with immunosuppressive therapy > 3 years

In the literature such immunosuppressed women had an increased risk of intraepithelial neoplasia of 20% compared with less than 5% for the general population. Severely immunocompromised women also had high rates of progression, recurrence and persistent of dysplastic abnormalities.

The guidelines recommend that if an immunosuppressed woman has a screen-detected abnormality (even if the lesion is low-grade) she should be referred for colposcopy. At colposcopy the whole of the lower genital tract will need evaluation. Follow-up should be annual and indefinite.

## Women exposed in utero to diethylstilboestrol

- Annual cytological screening and colposcopy of both cervix and vagina
- Start any time on request
- Continue indefinitely

3. DES-exposed women should be offered annual cytological screening and colposcopic examination of both the cervix and the vagina. Screening should begin any time at the woman's request and continue indefinitely.

## Post-hysterectomy (total)

- For documented benign reasons
  - No further screening needed
- Unknown smear history
  - Once a baseline "normal" smear has been obtained, no further screening is needed

There is often some confusion about the need for Pap smears post-hysterectomy. Basically, if a total hysterectomy was done for documented benign reasons (eg.fibroids or menorrhagia) then no further screening is needed.

If the woman has an unknown smear history prior to her hysterectomy, take a vault smear and once a baseline "normal" smear has been obtained, no further screening is needed.

If the woman retains her cervix, Pap smears should be taken as per usual.

## Post-hysterectomy

- Subtotal hysterectomy
  - Routine screening
- Hysterectomy because of CIN 2 or 3
  - Continue screening
- Hysterectomy for genital malignancy
  - Continue screening

Women who have had a sub-total hysterectomy still have a cervix and thus need to continue routine screening under the general guidelines. If the hysterectomy was done because of CIN 2 or 3, continued screening is recommended because of the increased risk of vaginal neoplasia. We don't yet know the role HPV testing may be able to play in these cases. Women who have had a hysterectomy because of genital malignancy should be under ongoing surveillance from a gynaecological oncologist.




The revised guidelines acknowledge that there will be women in exceptional circumstances who may wish to see a specialist earlier than recommended.

The guidelines acknowledge that a different management course may be adopted in exceptional circumstances

- The unduly anxious woman
- The woman who makes a specific request for specialist reassurance
- The geographically isolated woman

In such cases as the unduly anxious woman, the woman who makes a specific request for specialist reassurance and the geographically-isolated woman, the guidelines acknowledge that a different management course may be appropriate.



**Safety of the revised  
guidelines**



Will there be more cancers?

One important questions that has been asked concerning the revised guidelines is: “will there be more cervical cancers?”

## Any extra cancers?

Guidelines Review Group Executive	Oct 2004	Model estimated no extra cancers
Workshop of five independent epidemiologists	Nov 2004	Agreed most likely a neutral effect; any extra cancers would be microinvasive and curable

As many of you are aware, there was considerable debate, mainly in the media, about the possibility of the new 'low grade' guidelines leading to extra cancers. The Guidelines Review Group (GRG) considered this suggestion and the GRG executive model estimated NO extra cancers. A separate workshop was held with five independent epidemiologists, who were not involved with the guidelines development and they came to the conclusion that the revised guidelines would be safe for women, and that it was very unlikely there would be any extra cancers as a result.

The guidelines are not prescriptive to clinicians.

You can work with your patients to customize their management according to individual circumstances.

Finally I would like to remind you that these are **guidelines**. They make recommendations on best practice based on the latest available information. They aim to assist you to make informed decisions about the best management for your patients. Individual circumstances need to be considered. Issues such as the availability of specialist care, the likelihood of a woman returning for follow-up and a woman's anxiety levels can all impact on management decisions.

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The guidelines document is available at  
[www.nhmrc.gov.au/publications/synopses/wh39syn.htm](http://www.nhmrc.gov.au/publications/synopses/wh39syn.htm)  
To order free hard copies: [www.cancerscreening.gov.au](http://www.cancerscreening.gov.au)

The document can be found at this website, though viewers should be warned that it is around 180 pages in length!

The Department of Health and Ageing will provide hard copies at no cost.

These can be ordered from the website:  
[www.cancerscreening.gov.au](http://www.cancerscreening.gov.au)