Changes to the National Cervical Screening Program

KEY POINTS

From May 2017 changes will be introduced to the National Cervical Screening Program
Pap smears will be replaced with human papillomavirus (HPV) testing of cervical samples with partial HPV genotyping, and reflex liquid-based cytology (LBC) on samples testing positive for HPV; entry age will increase from 18 to 25 years, and the screening interval extended from 2 to 5 years.

Women aged 69–74
Women will be invited to screen until they are 69 years of age, and will be invited to exit the program if they have a further negative HPV test between 70 and 74 years of age.

Alternative sample collection option to be introduced for under-screened or never-screened women
To improve participation, self-collection of a cervical sample for HPV testing will also be available for under-screened or never-screened women.

A national register will be established
A national register for cervical screening will be established (currently being negotiated), replacing the current State- and Territory-based registries. Invitation and recall letters will be sent out to encourage participation.

New tests will be available on the Medical Benefits Schedule from May 2017 onwards
The new tests are not currently available on the MBS, but MBS subsidy will be in effect from May 2017 onwards.

Do not delay screening women under the current screening arrangements
For now, it is business as usual – do not delay the 2-yearly Pap smear test for women aged 18–69.

HPV-vaccinated women should be screened for cervical cancer
Remind HPV-vaccinated women of the importance of cervical screening, because the current HPV vaccine only protects against two HPV types that cause about 70% of cervical cancers.
EVIDENCE SNAPSHOT

For the first time since it was established in 1991, the National Cervical Screening Program (NCSP) will be renewed to focus on HPV testing that better identifies women at risk of pre-cancerous changes and cervical cancer.

Australia will be the second country in the world (after the Netherlands) to incorporate primary HPV testing into their national cervical screening program.

WHAT IS KNOWN ABOUT THIS TEST?

HPV testing with partial genotyping combined with LBC triage for HPV-positive women is an effective strategy for early detection of cervical abnormalities, with equivalent or better sensitivity, specificity and positive predictive value to that of the Pap smear.

A negative HPV test has a very high negative predictive value, allowing for a longer screening interval.

HPV tests may be DNA or RNA based.

AREAS OF UNCERTAINTY

HPV infection is associated with nearly all high-grade cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) and invasive cervical cancer.

However, it remains possible, though uncommon, that cervical cancer may go undetected in women who test negative for high-risk HPV genotypes, until symptoms appear. No screening test is 100% accurate.

Despite this possibility the renewed NCSP is predicted to reduce incidence and mortality from cervical cancer by at least 15%, which is a major improvement.

WHAT DOES NPS SAY?

Cervical screening with HPV testing detects the primary causal agent for the vast majority (99%) of cervical cancers, to enable early detection and closer monitoring of women who are at risk of progression to cervical cancer.

The high negative predictive value of the HPV test allows for screening every 5 years for HPV-negative women. Increasing the starting age to 25 will help reduce the risk of detecting transient HPV infection and regressive CIN.

MBS listing

From May 2017

MBS subsidy for the renewed NCSP will begin on 1 May 2017, when the HPV screening test with partial genotyping and reflex LBC will become available on the MBS.

The National Cancer Screening Register will be in place to support the renewed clinical pathway.

What is it?

It is now recognised that persistent infection with oncogenic HPV subtype/s (particularly 16 and 18) causes the vast majority of cervical cancers.1-7

While most HPV infections are transient and clear without intervention within 1–2 years,8 the infection can persist in up to 10% of women, leading to cervical intraepithelial neoplasia (CIN) and progression to cervical cancer over 10–15 years.1,7

By screening women for HPV infection, those at high risk of cervical cancer can be identified early to enable closer monitoring for cytological changes that precede invasive cervical cancer.

HPV testing with partial genotyping will allow for individual identification of two or three HPV genotypes most predominantly associated with cervical cancer (16, 18 ± 45), while other high-risk HPV genotypes will be detected as a pooled result.

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a It is currently unknown whether a negative HPV test result reflects a completely ‘cleared’ HPV infection, or whether the viral load has been reduced to undetectable levels.
Changes to the National Cervical Screening Program

Who is it for?
The starting age for women participating in the renewed NCSP will be increased to 25, and women will be invited to screen until they are 69.

Women will be invited to exit the program by having an HPV test between 70 and 74 years of age and may stop cervical cancer screening if their test result is negative.

Women who are under-screened or never-screened can use self-collection facilitated by a medical or nurse practitioner or other health professional, and women with symptoms (pain or bleeding) can request a cervical test at any age.

Where does it fit?
The 5-yearly HPV test with partial HPV genotyping will replace the Pap smear as the primary screening test for the NCSP.

If the HPV test result is negative, the patient will be recalled in 5 years for their next test. If the test is positive, the same sample will then proceed to LBC to determine if any cytological changes are apparent.

Women who test positive for certain high-risk HPV genotypes (HPV 16, 18 and possibly 45) will proceed directly to colposcopy, irrespective of the LBC result.

For women who test positive for other HPV genotypes, the results of the LBC will be used as a triage to determine the follow-up procedure. Clinical management guidelines are currently being developed to support the screening policy.

Using HPV as a more sensitive primary screening test will reduce the number of false-negative results. Following this with reflex LBC testing will reduce the number of false-positive results that could lead to unnecessary follow-up.

To improve participation by women who do not screen regularly or at all, self-collection of a vaginal sample will also be available for under-screened or never-screened women. Under-screened is defined as no test in the last 7 years.

Sampling must be facilitated by a medical practitioner, nurse practitioner or other health professional (on behalf of a medical practitioner).

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**Legend**

- **Primary test**
- **Reflex test**
- **Test result**
- **Comms of test result**

**Risk of cervical cancer precursors**

- **Lower**
- **Intermediate**
- **High**

**Recommendation**

- **MSAC recommendations**
  - (in development)

**Management Guidelines**

- **p/d LSIL**
- **Negative cytology**
- **Any positive HPV**
- **Indicates HPV infection still present**
- **Indicates cellular changes present that may require treatment**
- **Indicates high-risk HPV infection present**
- **Unsatisfactory test for technical reasons**

**Figure 1. The proposed cervical screening pathway.**

- **Negative HPV**
  - Recall for screening in 5 years

- **Positive HPV**
  - Reflex LBC
  - Positive HPV
    - HPV 16, 18 ± 45
    - HSIL
  - Other types
    - Repeat HPV test in 12 months
    - Any positive HPV
      - Refers for colposcopy with reflex LBC result

- **Negative cytology**
  - Recall for screening in 5 years

- **p/d LSIL**
  - Indicates HPV infection still present
  - Refers for colposcopy with reflex LBC result

- **Unsatisfactory test**
  - Retest within 6 weeks

**Indicates HPV infection still present**

- **Indicates cellular changes present that may require treatment**

- **Indicates high-risk HPV infection present**

- **Unsatisfactory test for technical reasons**

**Figure 1. The proposed cervical screening pathway.**
Changes to the National Cervical Screening Program

who also offers mainstream cervical screening. The proposed cervical screening pathway is shown in Figure 1.

Note that this proposed screening pathway/management protocol was derived from recommendations from the Medical Services Advisory Committee, and the final management protocol is currently under development and should be available in mid-2016.

The previous 2005 NHMRC document Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities will be superseded by the new management guidelines with the introduction of the renewed NCSP in May 2017.

How does it compare?

Improved sensitivity of detection for high-grade CIN (2 or worse)

Direct comparisons of HPV testing with cytology (Pap smear or LBC) in two randomised controlled trials demonstrated increased detection of CIN2 or worse (CIN2+) over subsequent screening rounds (1–5 years later) compared with women who were tested using cytology alone.10,11

Other RCTs also reported an increase in the sensitivity of detection for high-grade CIN (CIN2+, CIN3+) in the HPV testing arm compared with the cytology arm (Pap smear or LBC);12-15 however, these studies used HPV and cytology co-testing in the HPV arm rather than HPV testing alone.12-14

The HPV tests used in these RCTs identified high-risk HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68;11,13-15 plus, in one study, type 66.12 A positive HPV test, particularly for types 16 or 18, has been associated with increased incidence of CIN3 or worse (CIN3+) up to 10 years later when cervical abnormalities were left untreated.6

This was demonstrated in a prospective cohort study of 20,000 women, in which an HPV entry test was followed up cytologically to determine 10-year cumulative incidence rates of ≥ CIN3.

Features of a diagnostic test

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<th>Sensitivity – true positive rate (for disease)</th>
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<td>ie, how well does the test pick up people who have the condition?</td>
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<th>Specificity – true negative rate</th>
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<td>ie, how good is this test at correctly excluding people without the condition?</td>
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<th>Positive predictive value (PPV) – post-test probability of a positive test</th>
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<th>Negative predictive value (NPV) – indicates post-test probability of a negative test</th>
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<td>ie, if a person tests negative, what is the probability they do not have the condition?</td>
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This result was highest in women who were HPV-16-positive (17.2% [95% CI 11.5% to 22.9%]), followed by those who were HPV-18-positive (13.6% [95% CI 3.6% to 23.7%]), compared with 0.8% [95% CI 0.6% to 1.1%] in women who tested negative for high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68).16

Reduced incidence of future high-grade CIN and cervical cancer

Multiple studies have shown that early identification of women infected with high-risk HPV genotypes, and excisional treatment of high-grade cervical lesions (CIN2+), protected against future incidence of high-grade CIN13,14,18 and invasive cervical cancer.19

HPV testing provided 60–70% greater protection against invasive cervical cancers compared with cytology, with significantly reduced incidence of adenocarcinomas.19

Lower specificity of HPV testing necessitates more detailed approach to screening

The lower specificity and positive predictive value of HPV testing compared with cytology necessitates further testing with LBC to avoid unnecessary and invasive follow-up tests.

To increase specificity of HPV testing, partial genotyping will be used to help identify women at highest risk of progression to cervical cancer, and women with other high-risk HPV types will be triaged using LBC.
Partial HPV genotyping to identify women at highest risk of cervical cancer

There is strong evidence that women infected with HPV types 16 and 18 are at elevated risk of high-grade CIN and future development of cervical cancer, compared with women infected with other HPV types or those who are HPV negative.

Comprehensive data on worldwide HPV genotype distribution in patients with invasive cervical cancer showed that HPV 16, 18 and 45 together accounted for about 94% of HPV-positive cervical cancers.\(^{20,21}\)

HPV 16 was the most common and was found in 50.9% of HPV-positive cases, followed by HPV 18 (31.6%) and HPV 45 (11.6%).\(^{20}\)

Various studies have shown that HPV 16 and 18 are associated with CIN that are less likely to regress and more likely to progress to high-grade CIN compared with other HPV genotypes.\(^{22-24}\)

The separate identification of HPV 16 and 18 through partial HPV genotyping was shown to provide increased specificity for high-grade CIN compared with HPV testing without partial genotyping.\(^{26}\)

Increased specificity of screening with LBC triage

Based on the results of several RCTs, use of LBC to triage HPV-positive women in the renewed NCSP is likely to increase specificity and positive predictive value of HPV testing\(^{16}\) and should minimise the harms of primary HPV testing (see ‘Safety Issues’).\(^{9,11}\)

A systematic review found that, compared with conventional cytology using the Pap smear, LBC was not significantly different in terms of sensitivity and specificity for CIN2+ or CIN3\(^{+}\) but had distinct advantages including a reduced proportion of unsatisfactory samples\(^{28,29}\) and simplified logistics of screening.\(^{9,12}\)

Unlike the Pap smear, LBC can be performed on the same cervical sample as the HPV test,\(^{12}\) avoiding the need for patients to return for resampling if their HPV test is positive.\(^{9}\)

Two large RCTs have demonstrated that HPV testing with LBC triage has equal specificity and a higher positive predictive value for CIN2+ and CIN3+ compared with the Pap smear when considered across all age groups.\(^{10}\)

Using this triage approach, referrals to colposcopy were reduced in comparison with HPV testing alone,\(^{11}\) indicating that LBC triage should minimise unnecessary follow-up procedures.

Age for starting screening increased to 25 years

In younger women HPV infections are highly prevalent,\(^{10}\) with a higher incidence of high-grade cervical abnormalities.\(^{8}\) However, there is a very low incidence of, and mortality from, cervical cancer in women under 25.\(^{8}\)

High-grade cervical abnormalities can regress if left untreated.\(^{22,30}\) Composite data from studies published between 1950 and 1990 showed that almost one-half of CIN2 and one-third of CIN3 regressed over 1–25 years of follow-up.\(^{31}\)

There is strong evidence to suggest a higher risk of over-diagnosis and over-treatment of cervical abnormalities in younger women due to high incidence of transient HPV and regressive CIN.

Several RCTs have shown that specificity of HPV testing with\(^{13,15}\) or without LBC triage\(^{26}\) for detection of CIN2+ was lower in younger women than those in older age groups (≥ 30–34 years).

There is no evidence, in Australia or internationally, that cervical screening in women under 25 is effective or leads to reduced mortality from cervical cancer. This is in keeping with International Agency for Research in Cancer (IARC) recommendations that cervical screening should begin no earlier than age 25.\(^{32,33}\)

Based on the available evidence, the renewed NCSP will have a starting age of 25 to minimise the harms of over-diagnosis and over-treatment in women participating in HPV-based cervical screening.

Screening will be maintained until age 69; however, exit testing between the ages of 70 and 74 will be included in light of increasing life expectancy,\(^{14}\) in an age group where the benefits of screening outweigh the risks, and over-diagnosis is unlikely.\(^{9}\)
Extension of screening intervals to 5 years

Available evidence suggests screening intervals longer than those generally considered for cytology would be appropriate and safe for HPV testing, due to the test’s high negative predictive value and longitudinal sensitivity.

The high negative predictive value of HPV testing was demonstrated in a comparison with cytology through an extended follow-up of the ARTISTIC trial.35 Women who were HPV negative at baseline had a similar incidence of CIN2+ after 6 years (0.87%) to that after 3 years in women who were cytology negative at baseline (0.78%).35

A systematic review reported the negative predictive value of HPV testing as > 99% in most RCTs.27

A 13-year follow-up of the Swedescreen RCT demonstrated that extension of screening intervals for HPV testing did not compromise the sensitivity of the test, as detection of CIN2+ after 5 years (86.40% [95% CI 79.21% to 91.37%]) remained similarly sensitive to that for cytology after 3 years (85.94% [76.85% to 91.84%]).36

A 5-year screening interval for the renewed NCSP is safe, efficient and may help to reduce the potential harms of more frequent cervical screening, including over-diagnosis and over-treatment of regressive CIN lesions (see ‘Safety Issues’).37

What does this mean for health professionals?

Until the new program starts in 2017, 2-yearly Pap smear should be continued in women aged 18–69.

When the new program starts, health professionals will:

► still need to perform a vaginal speculum examination and take a cervical sample, but this will be a liquid-based sample using a kit provided by the laboratory

► place the sample in the provided vial and send it to the laboratory for processing

► receive a report from the laboratory containing a single recommendation for action, based on risk of the presence of precursor lesions for cervical cancer

► need to communicate the result to the patient and arrange follow-up if needed.

Safety issues

The higher prevalence of HPV infection and CIN in younger women, particularly those under 25, impacts on the specificity of HPV testing, potentially resulting in false positives.

The harms associated with false-positive results include anxiety associated with further tests,38 including colposcopy, and subsequent treatment that may cause unnecessary harm.37

Specifically, over-treatment of regressive lesions may lead to increased risk of pregnancy-related morbidity due to unnecessary excisional treatment of cervical lesions.37

To mitigate this risk and to ensure the benefits of cervical screening outweigh the harms, the renewed NCSP has incorporated several evidence-based approaches supporting improved specificity for high-grade CIN. These include:

► increasing entry age to 25 years

► use of partial HPV genotyping to identify and more closely monitor women with the two most common high-risk HPV-genotype infections

► use of LBC triage for HPV-positive women to increase specificity and reduce referrals to colposcopy

► extended 5-year screening intervals to target persistent HPV and non-regressive CIN.

Reason for MBS listing

Based on the strength of clinical evidence in relation to safety, clinical effectiveness and cost-effectiveness, the MSAC recommended listing of a 5-yearly primary HPV test with partial genotyping, and reflex LBC for HPV-positive results (for the renewed National Cervical Screening Program), to replace the 2-yearly Pap smear.
Information for patients

From May 2017, cervical screening will involve testing for the human papillomavirus (HPV) that causes most cases of cervical cancer. Infection with HPV leads to the pre-cancerous cellular changes that develop in the cervix, before progression to cervical cancer.

HPV testing is just as safe and more effective for early detection of cervical abnormalities than the Pap smear. Instead of detecting the cellular changes through the Pap smear, HPV testing will allow for early identification of women who are at higher risk of developing cervical cancer, so they can be monitored more closely and treated when necessary.

A vaginal examination will still be required, and you will notice no change to the examination and sampling technique during your visit as it is just like the Pap smear examination.

If you have a negative result, you do not need to be screened as often – you will be sent an invitation for screening in five years’ time.

If you have an abnormal test result, your doctor will advise the type of follow-up you require, which could be further testing or further investigation.

Until the new program is started in 2017 it is important that you still have your regular 2-yearly Pap smear if you are aged 18–69.

You still need to participate in cervical screening, even if you have been vaccinated for HPV – the vaccine does not protect against all the types of HPV that cause cervical cancer.
REFERENCES


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