
Application 1276

Final Decision
Analytic Protocol to
guide the assessment
of the National
Cervical Screening
Program Renewal

September 2012

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

Purpose of this document

This document is intended to provide a structure to a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the proposed structure. The final protocol will provide the basis for the assessment of the intervention.

The final protocol guiding the assessment of the health intervention will be developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the question for public funding that the assessment is intended to answer:

- Patients** – specification of the characteristics of the patients in whom the intervention is to be considered for use
- Intervention** – specification of the proposed intervention and how it is delivered
- Comparator** – specification of the therapy most likely to be replaced by the proposed intervention
- Outcomes** – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

The Department of Health and Ageing (DoHA), under the guidance of the Screening Subcommittee of the Australian Health Ministers' Advisory Council (AHMAC) is undertaking a 'renewal' of the National Cervical Screening Program (NCSP). The renewal is multi-tiered, allowing for consideration of screening tests and screening pathways; the impact of HPV vaccination; cost-effectiveness of different screening tests and pathways; use of data systems and quality mechanisms; and program acceptability. The cost and effectiveness of screening tests and screening pathways, in the context of the availability of HPV vaccination, are considered to be relevant to the assessment by MSAC and therefore DoHA as a joint applicant with the Screening Subcommittee has requested that a DAP be constructed. It is anticipated that the results of the renewal will alter the structure and function of the NCSP, to ensure that Australian women are provided with an optimal and sustainable cervical screening program.

Background

Population Based Screening

The World Health Organization defines screening as the presumptive identification of unrecognised disease or defects by means of tests, examinations or other procedures that can be applied rapidly. Screening is intended for all people, in an identified target population, who do not have symptoms of the disease or condition being screened for. The process can identify: disease pre-cursors; early disease; or disease markers. Screening intends to detect disease at an early stage when it can be better treated. Screening can reduce the risk of developing or dying from a disease, but it does not guarantee that disease will not occur, or if it occurs, that it can be cured. A 'positive' screening test identifies people who are at an increased likelihood of having the condition and who require further investigation to determine whether or not they have the disease or condition. (AHMAC 2008)

Population based screening is where a test is offered systematically to all individuals in a defined target population within a framework of agreed policy, protocols, quality management, monitoring and evaluation (AHMAC 2008). The target population is a clearly defined sub-group of the whole population that has been shown by strong scientific evidence to be most at risk of getting the disease and that will gain the most health benefit from early detection of the disease or its pre-cursors. Screening tests, like all tests, are never 100% accurate therefore most population based screening programs require the target population to be screened at regular intervals. There are three national population-based cancer screening programs in Australia: BreastScreen Australia, the National Cervical Screening Program, and the National Bowel Cancer Screening Program.

The Australian Government has developed a Population Based Screening Framework (AHMAC 2008), founded on the World Health Organizations principles of screening. The aim of the Framework is to provide guidance for decision makers when considering potential population based screening programs in Australia by outlining the requirements of population based screening.

Cervical Cancer in Australia

Cervical cancer affects the cells of the uterine cervix and may arise from the squamous cells that cover the outer surface of the cervix (known as squamous cell carcinoma) or from glandular cells in the cervical canal (known as adenocarcinoma). In Australia in 2008, 65.1% of cervical cancers were squamous cell carcinoma and 25.7% were adenocarcinoma, with adenosquamous (3.3%) and other cervical cancers (5.9%) making up the remainder (AIHW 2012). Cervical cancer is the 13th most common cancer affecting Australian women (excluding basal and squamous cell carcinoma of the skin). In 2008, for which the latest data is available, there were 9.3 new cases of cervical cancer and 1.9 deaths per 100,000 women aged 20 to 69 years. Incidence of cervical cancer and mortality is much higher in Aboriginal and Torres Strait Islander women, with incidence at 22.3 cases and death at 9.7 per 100,000 women in the period 2003 to 2007 (AIHW 2012).

In Australia, to combat cervical cancer, there is the National Cervical Screening Program (NCSP) and there is also a National HPV vaccination program (NHVP) which provides HPV vaccination to girls aged between 12 and 13 years through a school-based program. Details of these two programs are provided below.

Cervical screening – a secondary prevention strategy

Cervical screening was carried out opportunistically in Australia from the 1960s until 1991, when an organised screening program was introduced, now called the National Cervical Screening Program (NCSP). The NCSP is jointly funded by the Australian and state and territory governments and sets out the following policy for screening:

- Routine screening with Pap smears should be carried out every two years for women who have no symptoms or history suggestive of cervical pathology.
- All women who have ever been sexually active should start having Pap smears between the ages of 18 to 20 years, or one or two years after first having sexual intercourse, whichever is later.
- Pap smears may cease at the age of 70 years for women who have had two normal Pap smears within the last five years. Women over 70 years who have never had a Pap smear, or who request a Pap smear, should be screened.

This policy applies only to women without symptoms that could be due to cervical pathology. Women with a past history of high-grade cervical lesions, or who are being followed up for a previous abnormal smear are managed in accordance with the 2005 National Health and Medical Research Council Guidelines: *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities* (the Guidelines).

Since the introduction of the NCSP the incidence of cervical cancer has dropped from 17.2 per 100,000 women in 1991 in the target age group (20-69 years) to 9.3 in 2008. The mortality rate from cervical cancer has also dropped in the target age group, from 4.0 per 100,000 women in 1991 to 1.9 in 2007 (AIHW 2012). Participation rates exceed 55% and 70% within two and three year intervals respectively for women in the target age group and over 80% of the target age group have had a Pap smear within five years (AIHW 2012).

Conventional cervical cytology (or Pap smear) is primarily provided through general practice and other primary healthcare settings with rebates available from the Medicare Benefits Schedule (MBS). The

current MBS item descriptor for conventional cervical cytology (for screening and non-screening purposes) and HPV DNA testing (for follow up of treated high grade abnormalities) is outlined in Table 1.

Table 1: Current MBS Item descriptors for cervical cytology and HPV DNA testing

<p>Item number 73053</p> <p>Cytology of a smear from cervix where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each examination</p> <p>(a) for the detection of precancerous or cancerous changes in women with no symptoms, signs or recent history suggestive of cervical neoplasia, or</p> <p>(b) if a further specimen is taken due to an unsatisfactory smear taken for the purposes of paragraph (a); or</p> <p>(c) if there is inadequate information provided to use item 73055;</p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p> <p>(See para P16.11 of explanatory notes to this Category)</p>
<p>Item number 73055</p> <p>Cytology of a smear from cervix, not associated with item 73053, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test</p> <p>(a) for the management of previously detected abnormalities including precancerous or cancerous conditions; or</p> <p>(b) for the investigation of women with symptoms, signs or recent history suggestive of cervical neoplasia;</p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p> <p>(See para P16.11 of explanatory notes to this Category)</p>
<p>Item number 73057</p> <p>Cytology of smears from vagina, not associated with item 73053 or 73055 and not to monitor hormone replacement therapy, where the smear is prepared by direct application of the specimen to a slide, excluding the use of liquid based slide preparation techniques, and the stained smear is microscopically examined by or on behalf of a pathologist - each test</p> <p>Fee: \$19.60 Benefit: 75% = \$14.70 85% = \$16.70</p> <p>(See para P16.11 of explanatory notes to this Category)</p>
<p>Explanatory notes P16.11 Cervical and Vaginal Cytology - (Items 73053 to 73057)</p> <p>Item 73053 applies to the cytological examination of cervical smears collected from women with no symptoms, signs or recent history suggestive of cervical neoplasia as part of routine, biennial</p>

examination for the detection of pre-cancerous or cancerous changes. This item also applies to smears repeated due to an unsatisfactory routine smear, or if there is inadequate information provided to use item 73055.

Cytological examinations carried out under item 73053 should be in accordance with the agreed National Policy on Screening for the Prevention of Cervical Cancer. This policy provides for:

- (i) an examination interval of two years for women who have no symptoms or history suggestive of abnormal cervical cytology, commencing between the ages of 18 to 20 years, or one to two years after first sexual intercourse, whichever is later; and
- (ii) cessation of cervical smears at 70 years for women who have had two normal results within the last five years. Women over 70 who have never been examined, or who request a cervical smear, should be examined.

This policy has been endorsed by the Royal Australian College of General Practitioners, the Royal Australian College of Obstetricians and Gynaecologists, The Royal College of Pathologists of Australasia, the Australian Cancer Society and the National Health and Medical Research Council.

The *Health Insurance Act 1973* excludes payment of Medicare benefits for health screening services except where Ministerial directions have been issued to enable benefits to be paid, such as the Papanicolaou test. As there is now an established policy which has the support of the relevant professional bodies, routine screening in accordance with the policy will be regarded as good medical practice.

The screening policy will not be used as a basis for determining eligibility for benefits. However, the policy will be used as a guide for reviewing practitioner profiles.

Item 73055 applies to cervical cytological examinations where the smear has been collected for the purpose of management, follow up or investigation of a previous abnormal cytology report, or collected from women with symptoms, signs or recent history suggestive of abnormal cervical cytology.

Items 73057 applies to all vaginal cytological examinations, whether for a routine examination or for the follow up or management of a previously detected abnormal smear.

For cervical smears, treating practitioners are asked to clearly identify on the request form to the pathologist, by item number, if the smear has been taken as a routine examination or for the management of a previously detected abnormality.

Item number 69418

A test for high risk human papillomaviruses (HPV) in a patient who:

- has received excisional or ablative treatment for high grade squamous intraepithelial lesions (HSIL) of the cervix within the last two years; or
- who within the last two years has had a positive HPV test after excisional or ablative treatment for HSIL of the cervix; or
- is already undergoing annual cytological review for the follow-up of a previously treated HSIL.

- to a maximum of 2 of this item in a 24 month period

(Item is subject to rule 25)

Fee: \$64.00 **Benefit:** 75% = \$48.00 85% = \$54.40

HPV vaccination – a primary prevention strategy

Australia was one of the first countries to introduce a national HPV vaccination program. There are two vaccines available, which protect against the two types of HPV that cause approximately 70-80% of cervical cancer cases. The NHVP commenced in April 2007 and provides free HPV vaccinations through school-based programs, to girls aged between 12 and 13 years. The Australian Government also funded a two-year catch-up program for 13 to 18 year old girls in schools and 18 to 26 year old women, which was delivered through general practitioners.

It is anticipated that the HPV vaccine will decrease the number of abnormalities detected and the number of cases of cervical cancer, initially in the youngest women in the screening target age group, although since cervical cancer peaks in women over the age of 45-50 years, it will be some years before the full effects of vaccination are manifested.. However, the HPV vaccine protects only against two oncogenic HPV types, 16 and 18. While these two types are detected in 70% to 80% of cervical cancers in Australia (Brotherton 2008) there remains the possibility of cervical cancer due to other types. Consequently, cervical screening remains a key component of prevention and DoHA currently recommends the following: "Women, whether vaccinated or unvaccinated, should be screened for cervical cancer in accordance with the policy of the National Cervical Screening Program and the NHMRC Screening to prevent cervical cancer Guidelines for the management of asymptomatic women with screen detected abnormalities" (DoHA 2011).

Based on the standard indicator to measure HPV vaccine coverage, the proportion of girls vaccinated with three doses of HPV vaccine by 15 years, there was coverage of 70.8% in 2009 in Australia. The impact of HPV vaccination on the screening program should be taken into consideration when assessing the most appropriate cervical screening pathway for the future. Estimation of the impact of HPV vaccination on the NCSP will require modelling.

Male vaccination was also recommended in late 2011 and it was announced in June 2012 that boys will be vaccinated from 2013. This will have an incremental effect on infection rates in women, via the effects of herd immunity, and thus should be taken into account in modelled analysis of the impact of HPV vaccination on cervical infections and abnormality rates.

Renewal of the NCSP

The Australian cervical screening policy is thought to be quite intensive in comparison to international programs. In 2005, the International Agency for Research on Cancer (IARC) recommended that cervical screening should cover women aged 25 to 65 years and that women should undergo screening once every three years up to the age of 49 and every five years thereafter. When the NHMRC approved the Guidelines in June 2005, it recommended the screening interval in Australia be reviewed. Furthermore, the Senate Community Affairs Reference Committee recommended in its 2005 *Report on the inquiry into services and treatment options for persons with cancer*, that the target age

groups for the NCSP be reviewed regularly. The Screening Subcommittee agreed in 2007 that a review of the screening age range and interval should be placed on the committee work plan as a result of these recommendations. Consequently, DoHA is managing the Renewal of the NCSP under the auspice of the Screening Subcommittee of AHMAC and with advice and direction from an advisory group called the Renewal Steering Committee.

The Screening Subcommittee has indicated that the renewal will be undertaken in stages and will explore evidence relating to screening for cervical cancer, including the age range and frequency of screening, as well as the technologies used; cost effectiveness of cervical screening pathways for HPV immunised and non-immunised populations; data collection systems; registry functions; and program acceptability. The first two stages are being conducted through the MSAC process and will review the evidence for cervical screening pathways and undertake an economic evaluation.

More information on the Renewal may be found on the cancer screening website at www.cancerscreening.gov.au.

Intervention

Liquid Based Cytology (LBC)

Liquid based cytology is a method of preparing cervical samples for examination in the laboratory. The sample is collected in a similar way to conventional cytology however the head of the spatula, broom or brush containing the cells is broken or rinsed into a vial containing preservative liquid. The sample is then sent to the laboratory for processing to remove obscuring material such as mucous, pus or blood before being placed on a slide.

There are currently two LBC systems available in Australia. These two systems use different technical methods for processing the cells before placement on a slide. One uses a cell filtration system (ThinPrep® Pap system, Hologic [Australia] Pty Ltd) and the other a cell enrichment system (SurePath™ LBC system, Beckton Dickinson Pty Ltd). Automated image analysis can also be used with LBC, which allows the cytotechnologist to be directed to an area on the slide that is most likely to contain abnormal cells. Automated image analysis aims to reduce the time required to read a slide and reduce detection error.

MSAC has previously considered LBC and automated image analysis on a number of occasions. Details of these assessments are provided in Attachment 1. The 2002 assessment found that there was insufficient evidence to determine whether LBC was equal or superior in effectiveness compared to conventional cytology. The model used indicated that LBC was associated with greater costs per woman than conventional cytology. Since there was insufficient evidence to support a claim that LBC is superior to conventional cytology in detecting high-grade lesions or invasive cancer, there was no evidence to suggest that LBC would be cost-effective at the proposed price and MSAC advised there was insufficient evidence to support public funding of LBC for cervical screening.

In 2003 MSAC considered the safety, effectiveness and cost-effectiveness of automated image analysis for cervical screening cytology compared with manual processing (see Attachment 3 for details of this assessment). MSAC determined there was insufficient evidence to assess whether

automated image analysis is as effective as manual processing for cervical screening cytology. Given the lack of clinical evidence, an economic evaluation was not conducted and MSAC advised that there was insufficient evidence to support public funding of automated image analysis for cervical screening.

The 2009 assessment considered LBC using automated image analysis systems as well as manual LBC. The available evidence demonstrated that manual LBC compared to conventional cytology provided no statistically significant increase in sensitivity or specificity. Automated LBC detected more CIN 2+ lesions compared to conventional cytology, but results from one trial raised uncertainty about whether this difference is attributable to LBC alone, to the automation-assisted reading system or a combination of both. A modelled analysis found that automated LBC would be associated with a cost of \$194,835 per life year saved (LYS). Manual LBC was associated with a cost of \$126,315 per LYS to \$385,982 per LYS, depending on the level of reimbursement. MSAC concluded LBC is at least as effective as conventional cytology, but is not cost effective at the price requested and should not be supported for public funding.

The applicants have indicated that re-assessment of LBC may be beneficial alongside a review of the cervical screening age range and interval and HPV DNA testing.

HPV DNA testing

There are over 100 different types of HPV. Some of these, collectively referred to as oncogenic types, have been linked to the development of cervical abnormalities and cervical cancer. HPV DNA tests detect the genetic material of oncogenic types of HPV associated with cervical cancer. The NHMRC Guidelines recommend HPV DNA testing for women who have undergone treatment for high grade cervical abnormalities to monitor the effectiveness of treatment. An MBS item is available for this purpose. HPV DNA testing for any other purpose is not currently recommended by the NCSP and a Medicare rebate is not available.

Currently, in Australia HPV DNA testing is generally undertaken using a pooled method that tests for a number of different oncogenic types, to give an overall result of positive or negative. Although tests that provide full genotyping information for the specific HPV type(s) present are important for epidemiologic studies, they are generally not appropriate or validated for clinical use. However, increasingly, clinically-positioned HPV DNA tests which provide a partial genotyping facility to signal the presence of the most common types implicated in cancer (such as HPV 16/18), as distinguished from grouped 'other oncogenic' HPV types, are becoming available.

HPV DNA TESTING AS A TRIAGE TOOL

In 2002 MSAC considered the use of HPV DNA testing as a triage tool. Full details of the assessment are provided in Attachment 2. The evidence provided indicated that HPV DNA testing was more sensitive but less specific than cytology, although the evidence did not support widespread implementation. The assessment concluded that additional high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, would be useful in allowing a valid and reliable judgement of the sensitivity and specificity of HPV DNA testing. A decision analytic model indicated that HPV DNA testing was both more expensive and less effective in detecting high-grade lesions than the management plan currently recommended by the NHMRC, but the model was particularly sensitive to the estimated prevalence of high-grade lesions in women. MSAC advised that

there was currently insufficient evidence to support public funding at the time for the use of the HPV DNA test for triaging of women with equivocal cervical screening results.

In 2009 HPV DNA testing as a triage tool was re-assessed. Details of this assessment are provided in Attachment 2. Comparative accuracy studies provided strong evidence that an immediate HPV DNA triage test is a more sensitive test than a single repeat cytology test for detecting cervical intraepithelial neoplasia (CIN) 2+ lesions in women with low grade squamous intraepithelial lesion (LSIL), and has similar specificity to cytology pLSIL, but lower specificity than cytology dLSIL. Restricting the HPV DNA triage test to older age groups is associated with higher specificity and a lower colposcopy referral rate, but a smaller gain in sensitivity, compared with its use in all age groups. A modelled analysis predicted that, compared with current practice, a strategy of performing the HPV DNA triage test for women aged 30+ years produces an incremental cost-effectiveness ratio (ICER) of \$75,739 per life year saved (LYS) if conventional cytology is used with co-collection for HPV DNA testing; or \$83,496 per LYS using manual liquid based cytology (LBC) with reflex HPV DNA testing; or \$170,209 per LYS using automated LBC with reflex HPV DNA testing. On the basis of the available results, MSAC advised that HPV DNA triage testing in cervical cancer was not cost effective in the Australian setting at the current price of HPV DNA testing and MSAC did not support public funding.

HPV DNA TESTING AS A PRIMARY SCREENING TEST

In 2003 MSAC considered the use of HPV DNA testing for cervical screening as either a stand-alone screening test or combined with screening by cytology. Details of the assessment are provided in Attachment 2. MSAC found that there was insufficient evidence that HPV DNA testing is effective in detecting high grade cervical lesions when used as either a stand-alone screening test or combined with screening by cytology. Due to the lack of clinical evidence, an economic evaluation was not conducted.

The applicants have indicated that this technology should be re-assessed in conjunction with the consideration of changes in screening age and interval. There is current evidence available addressing the use of HPV DNA testing, in particular several international randomised controlled trials of primary HPV DNA screening compared to cytology have now reported several years of follow-up over two or three rounds of screening (Kitchener et al 2011, Ronco et al 2010; Mayrand et al 2007; Rijkaart et al 2012; Naucler et al 2009).

HPV DNA TESTING – PRACTITIONER VS. SELF-COLLECTED SAMPLES

HPV DNA testing using self collected samples has been studied as a strategy to reach underscreened populations. Self collection is a method where women can collect a sample of their own cells, usually using a tampon or cotton-tipped swab, for HPV DNA testing. Self collection may be undertaken within or outside (such as at home) a health care setting. The sample is sent to a laboratory for processing and testing. Self collection within a health care setting is widely used to test for Chlamydia and gonorrhoea infection.

The previous assessments of HPV DNA testing by MSAC have not considered the use of practitioner collected versus self-collected samples. The applicants have indicated it may be useful to consider self

collected samples for HPV DNA testing for underscreened and unscreened women, to supplement the organised screening program using practitioner collected samples for HPV DNA testing.

Other technologies

Horizon scanning of new and emerging technologies for DoHA are usually undertaken through the Australia New Zealand Horizon Scanning Network however it is recognised that there may be other technologies which could be considered in the NCSP that have not been identified in this draft DAP. The public consultation may identify other technologies that could be considered.

Frequency of cervical screening

Under the NCSP the recommended frequency of screening is every two years. The applicants have indicated that the frequency of screening requires review, particularly in light of international recommendations, i.e., those of IARC that suggest screening every three years from age 25 to 49 and then every five years for ages 50 to 65. Table A5.1 in Attachment 5 provides a summary of the screening intervals used in a range of countries that use cytology as the primary screening test (LBC or conventional), including New Zealand, the UK, the US, Canada and many European countries. In New Zealand and the UK screening is conducted every three years. In Canada and the USA testing is more frequent for younger women, but in Canada once there are two normal cytology tests, screening moves to every 3 years and in the US, the USPSTF recommends screening for cervical cancer in women age 21 to 65 years with cytology (Papanicolaou smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years (Moyer 2012). Screening frequency varies across Europe, however a three-yearly interval is common.

The frequency of screening will be dependent on the technology used as the primary screening test and longer screening intervals have been studied for HPV DNA testing. The multi-national pooled analysis of cohort study data by Dillner *et al* (2008) included seven primary HPV screening studies in six European countries and assessed long term cumulative incidence of CIN3+ over six years. The authors concluded 'that cervical screening strategies in which women are screened for HPV every six years are safe and effective'.

Regulatory status of new technologies

The Therapeutic Goods Administration (TGA) provides the regulatory framework for in-vitro diagnostic (IVD) medical devices. These include 'pathology tests and associated instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decision concerning clinical management' (TGA 2011). The framework came into effect on 1 July 2010. All IVDs supplied prior to 1 July 2010 are provided with a four year transition period (i.e. until 30 June 2014) to be brought into the regulatory framework. It would be expected that all products assessed and used as part of the NCSP would comply with the new regulatory framework. Manufacturers will be required to provide evidence that their product complies with the framework for their product to be claimed through the MBS.

Patient Population

Under the NCSP it is recommended screening should commence for all sexually active women between the ages of 18 and 20, or one to two years after first having sexual intercourse, whichever is later; and that 2-yearly screening should cease at age 70. It has been suggested by the applicant that the recommendations of IARC should be considered. The recommendations made by IARC in 2005 suggest that cervical screening should cover women aged 25 to 65 and that women should undergo screening once every three years up to the age 49 and then every five years thereafter. A recent UK study (Sasieni et al., 2009) assessed the effectiveness of cervical screening by age and concluded that cervical screening in women aged 20 to 24 has little or no impact on rates of invasive cervical cancer up to age 30, however some uncertainty exists regarding its impact on advanced stage tumours in women under age 30. In contrast, screening older women leads to a substantial reduction in incidence of and mortality from cervical cancer. Available information (see Table A5.1 in Attachment 5) indicates that, with the exception of Canada and some European countries, the commencement age for screening is generally around 25 years of age.

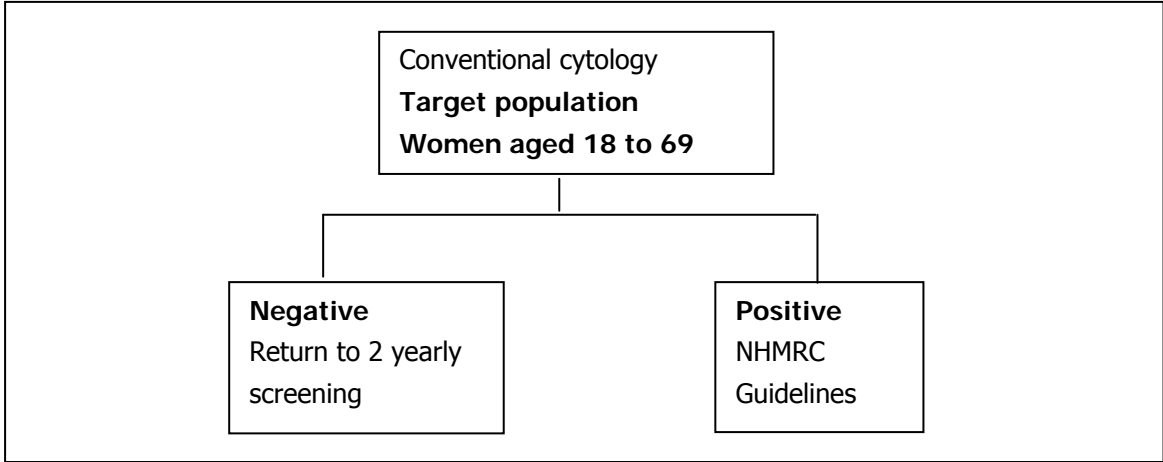
The applicants have indicated that the age range for cervical screening should be reviewed in this assessment. While the current screening program recommends that cervical screening may cease at the age of 70 years for women who have had two normal cytology tests within the last five years, it should be recognised that the lifetime impact of regular cervical screening will benefit older women past the exit age for the program. Therefore it will be important to ensure the assessment captures this positive effect on older women outside the target population.

Comparator

The comparator for any alternative cervical screening pathway is the current pathway promoted by the NCSP. All women between the ages of 18 (or one to two years after first having sexual intercourse, whichever is later) and 70 years of age should be screened every 2 years using conventional cytology.

Current algorithm

Figure 1: Algorithm for the current cervical screening program



Clinical Claim

NCSP policy has not been reviewed since the program was established over 20 years ago however the environment in which the NCSP operates has changed. Scientific understanding of cervical cancer has advanced, the HPV vaccine has been introduced, and new evidence is available in relation to screening intervals, types of screening tests, and the commencement age for screening. The applicant has proposed that LBC and HPV DNA testing should be re-assessed by MSAC alongside a review of cervical screening age range and interval and in the context of HPV vaccination where the proportion of women vaccinated against HPV types 16 and 18 will increase over time.

The IARC is an agency of the World Health Organization that promotes cancer research internationally. In 2004, an IARC Working Group evaluated the effectiveness of cervical screening in reducing cervical cancer incidence and mortality (IARC 2004). The findings indicated that cervical screening programs should include women aged 25-65 years, and that for acceptable effectiveness and efficiency, screening using cervical cytology (either conventional or LBC) should be undertaken at three year intervals up to the age of 49 years and at 5-yearly intervals thereafter. Many developed countries have adopted similar screening age range and intervals to the IARC recommendations and have achieved comparable incidence and mortality rates to those seen in Australia.

The applicant has indicated that the impact of HPV vaccination should be considered, i.e., if the current screening program serves as the comparator, then the comparison should be made with and without the modelled impact of HPV vaccination. A static model would use contemporary data on cervical screen-detected abnormality rates and related characteristics. A dynamic model (based on a birth age cohort approach) would account for the anticipated impact of HPV vaccination on cervical abnormality rates, which is likely to be seen emerging at the completion of the NCSP Renewal. This second model would allow a futuristic approach to inform changes in the cervical screening environment.

Outcomes and healthcare resources affected by introduction of proposed intervention

Outcomes

1. Health:
 - Incidence of cervical cancer
 - Cervical cancer mortality (age- and type-specific rates)
 - Morbidity and socio-economic effects of disease associated with oncogenic HPV types
2. Diagnostics:
 - Accuracy of detecting cancer, histologically confirmed HSIL (CIN2/3), ACIS and glandular cell changes – sensitivity, specificity, positive and negative predictive values, true positive, false positive, incremental rate of true positive, incremental rate of false positive
 - Accuracy of detecting histologically confirmed low grade disease (CIN1/ LSIL) – sensitivity, specificity, positive and negative predictive values, true positive, false positive, incremental rate of true positive, incremental rate of false positive
 - Proportion of lesions detected in each cytological category
 - Proportion of samples yielding unsatisfactory results
3. Patient outcomes:
 - quality of life, patient preference, satisfaction/anxiety (from screening and results from screening), patient compliance, safety/adverse events such as complications, impact on fertility and/or obstetric complications, avoidance of unnecessary treatments

The primary research questions will need expressly to bring out the benefit and harms (sometimes referred to as risks) in the different outcomes from the test in young women. For example, in assessing safety the physical and psychological effects on the screened individual of detected or not detected of precancerous lesions should be considered, including more intensive follow-up tests, consequences for fertility and also the effects on screened individuals of false test results (both false negatives and false positives).

Healthcare resources

The health care resources required for each primary question will need to be identified once the structure is finalised.

If the proposed structure (as outlined below) is accepted the assessment would include resources associated with:

- cervical cytology (conventional and LBC), including consultation costs and any triage test;
- HPV DNA testing including consultation costs and any triage test;
- the follow-up of abnormal test results including colposcopy; and
- treatment of high grade lesions and cancer.

Proposed structure for the assessment

It is proposed that the comparative safety, effectiveness and cost-effectiveness of three specific screening scenarios be addressed using the present screening program as the comparator. In addition, there would be a series of relevant secondary questions for each scenario. This would provide results for different protocol combinations for comparative analysis. Sensitivity analysis around 'a priori' assumptions would be included. If the evidence review indicates different parameters to those proposed, these will be included in the economic analysis.

The three screening scenarios are based on the primary screening tool or intervention. The first scenario maintains the current screening tool, conventional cytology, with a different target age range and screening interval. The second scenario introduces LBC to the screening program with a different target age range and screening interval. The third scenario introduces HPV DNA testing to the screening program with a different target age range and screening interval. It should be noted that all the options for using HPV DNA testing in the NCSP would also require that LBC be used.

The three scenarios will be assessed sequentially and form a matrix. This is depicted in the table below.

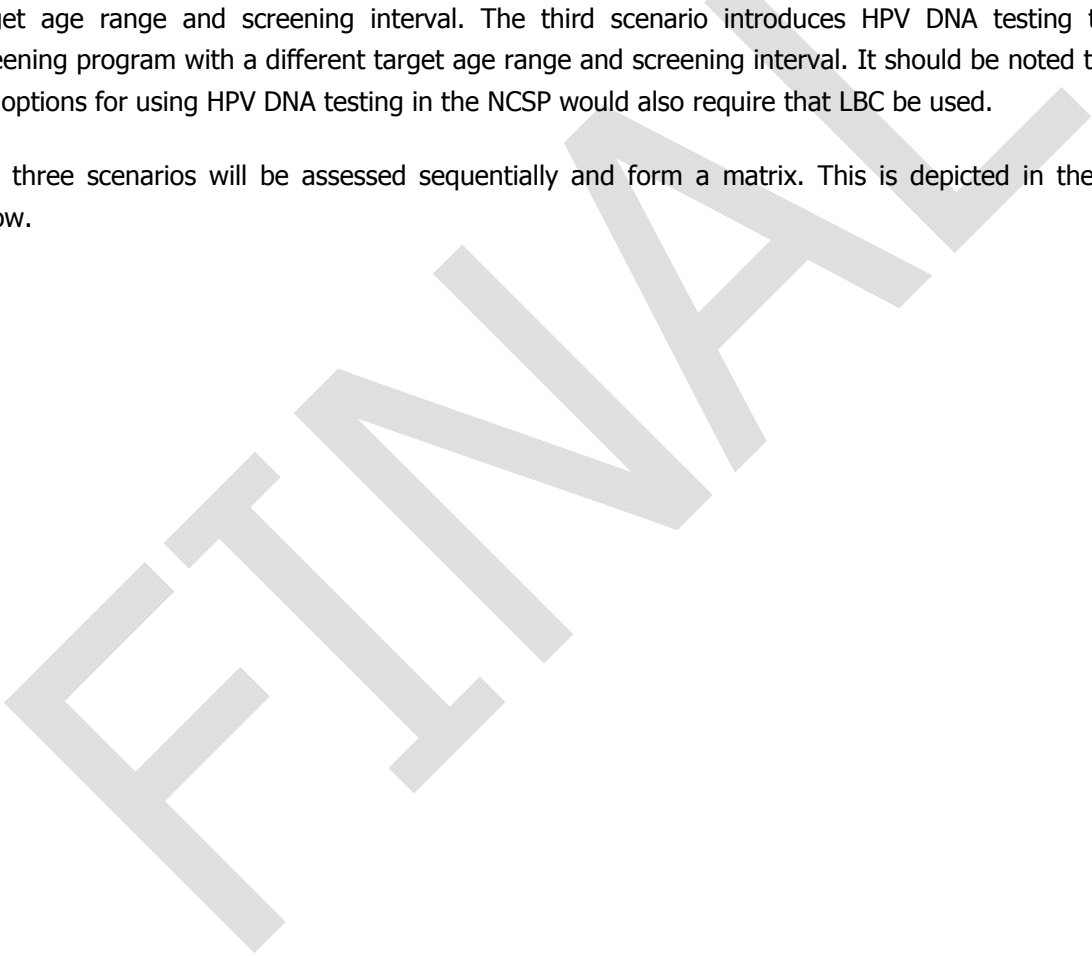


Table 2: Summary of cervical screening scenarios to be compared with the current cervical screening program*

	Comparator Current program	Scenario 1	Scenario 2	Scenario 3	
Primary Question	Primary screening test	Conventional cytology	Conventional cytology	LBC (cell filtration and cell enrichment separately)	HPV DNA testing (including information on genotyping separately)
	Age range	Women aged 18-69 years	Women aged 25-64 years (IARC recommendations)		
	Interval	2 years	3 years (aged 25-49) and 5 years (aged 50-65) (IARC recommendations)		No less than 5 years (a range of intervals should be considered)
Secondary Questions	Triage options**	<u>pLSIL/LSIL result</u> N/A (as per NHMRC Guidelines)	<u>pLSIL/LSIL result</u> N/A (as per NHMRC Guidelines)	<u>pLSIL/LSIL result</u> +/- reflex HPV DNA testing	<u>HPV positive result</u> 1) +/- LBC co-testing 2) +/- LBC reflex testing
	Additional technology	N/A	N/A	+/- Automated image analysis	
	Exit strategy	Must have two normal cytology tests within the last 5 years	HPV DNA test at age 64 years		
	Self collection	N/A	N/A		YES
	Invitation and recall system	N/A (overdue reminders only)	YES		

* With and without the modelled impact of HPV vaccination (static and dynamic models).

** In this assessment triage tests include additional tests undertaken in the laboratory, using the original sample, which will assist in making a final recommendation on the index test, based on the combined results. This does not involve tests for the follow-up of an abnormal result.

Primary Question 1 – Conventional cytology

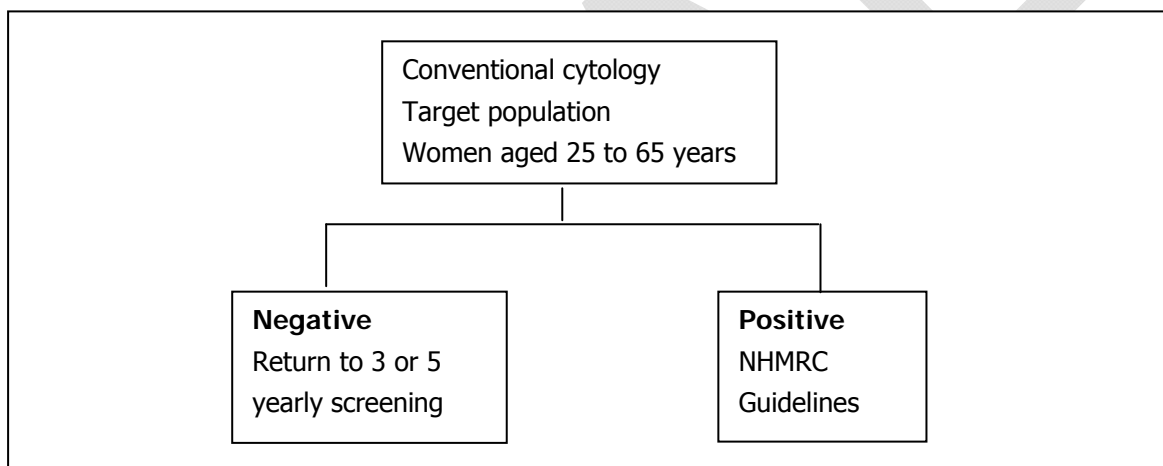
What is the comparative safety, effectiveness and cost-effectiveness of conventional cytology, using the IARC recommendations for age range and interval, compared with the protocol used in the current Australian cervical screening program?

SECONDARY QUESTIONS (SCENARIO ANALYSES)

- 1) What is the safety, effectiveness and cost-effectiveness of using one HPV DNA test for women exiting the program at age 65 years and over, compared with the existing protocol?
- 2) What is the cost-effectiveness of the pathway if an invitation/recall system was introduced, compared with the existing overdue reminder system without invitation?

PROPOSED ALGORITHM

Figure 2: Proposed algorithm for primary question 1



Primary Question 2 – Liquid Based Cytology

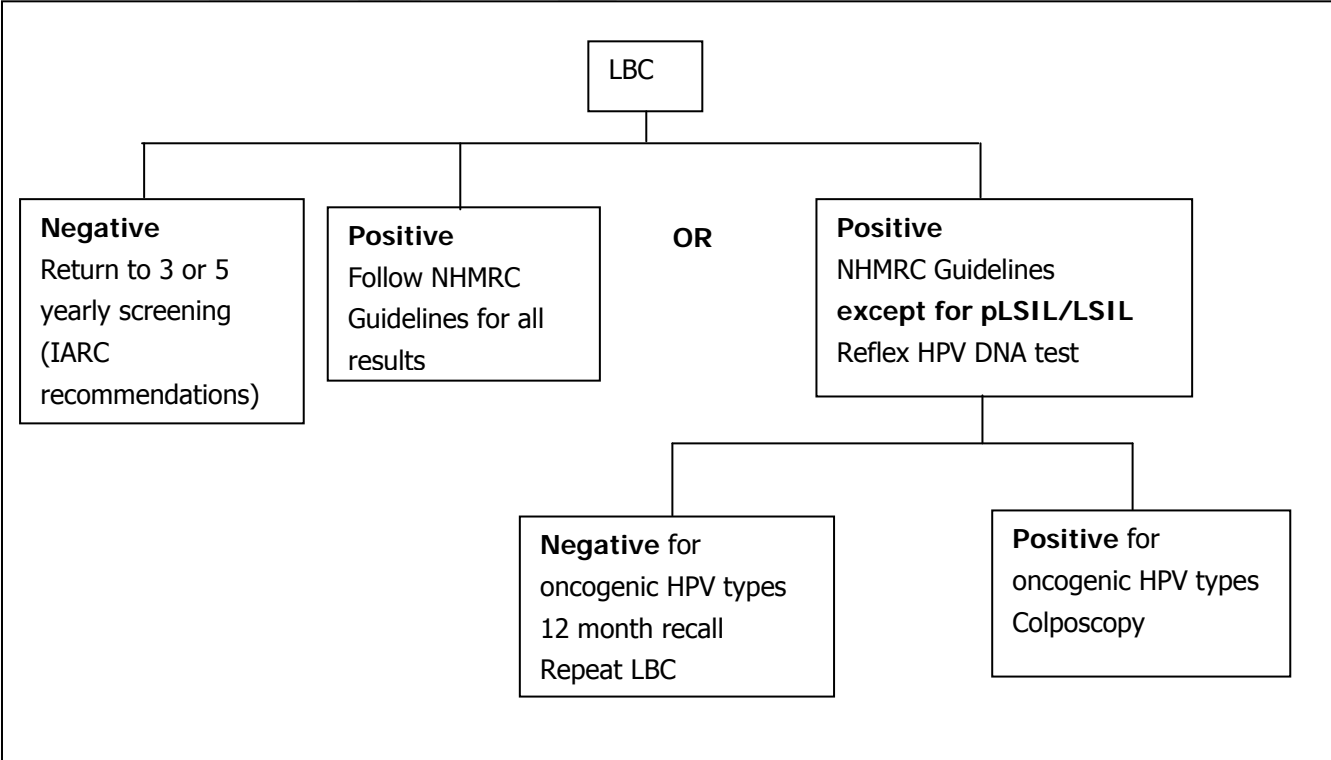
What is the comparative safety, effectiveness and cost effectiveness of either filtration or cell enrichment LBC¹ (using the IARC recommendations for age range and interval for cytology), compared with the protocol used in the current Australian cervical screening program?

SECONDARY QUESTIONS (SCENARIO ANALYSES)

- 1) What is the comparative safety, effectiveness and cost-effectiveness of using automated image analysis under Question 2 parameters, compared with the existing protocol?
- 2) What is the comparative safety, effectiveness and cost effectiveness of adding an HPV DNA test to triage women with pLSIL/LSIL, compared with the existing protocol?
- 3) What is the comparative safety, effectiveness and cost-effectiveness of using one HPV DNA test for women exiting the program at age 65 years and over, compared with the existing protocol?
- 4) What is the comparative safety, effectiveness and cost-effectiveness of undertaking a colposcopy immediately in comparison to delaying the test in women who have pLSIL/LSIL cytology and a positive HPV DNA test?
- 5) What is the comparative cost-effectiveness of the pathway if an invitation/recall system is introduced, compared with the existing recall system without invitation?

PROPOSED ALGORITHM

Figure 3: Proposed algorithm for primary question 2



to each other.

Primary Question 3 – HPV DNA testing

What is the comparative safety, effectiveness and cost-effectiveness of HPV DNA testing as the primary screening test in women aged 25 to 65 years every 5 years², compared with the protocol used in the current Australian cervical screening program? (this would include information on partial genotyping HPV tests/stratifying by the highest risk HPV genotypes)

SECONDARY QUESTIONS (SCENARIO ANALYSES)

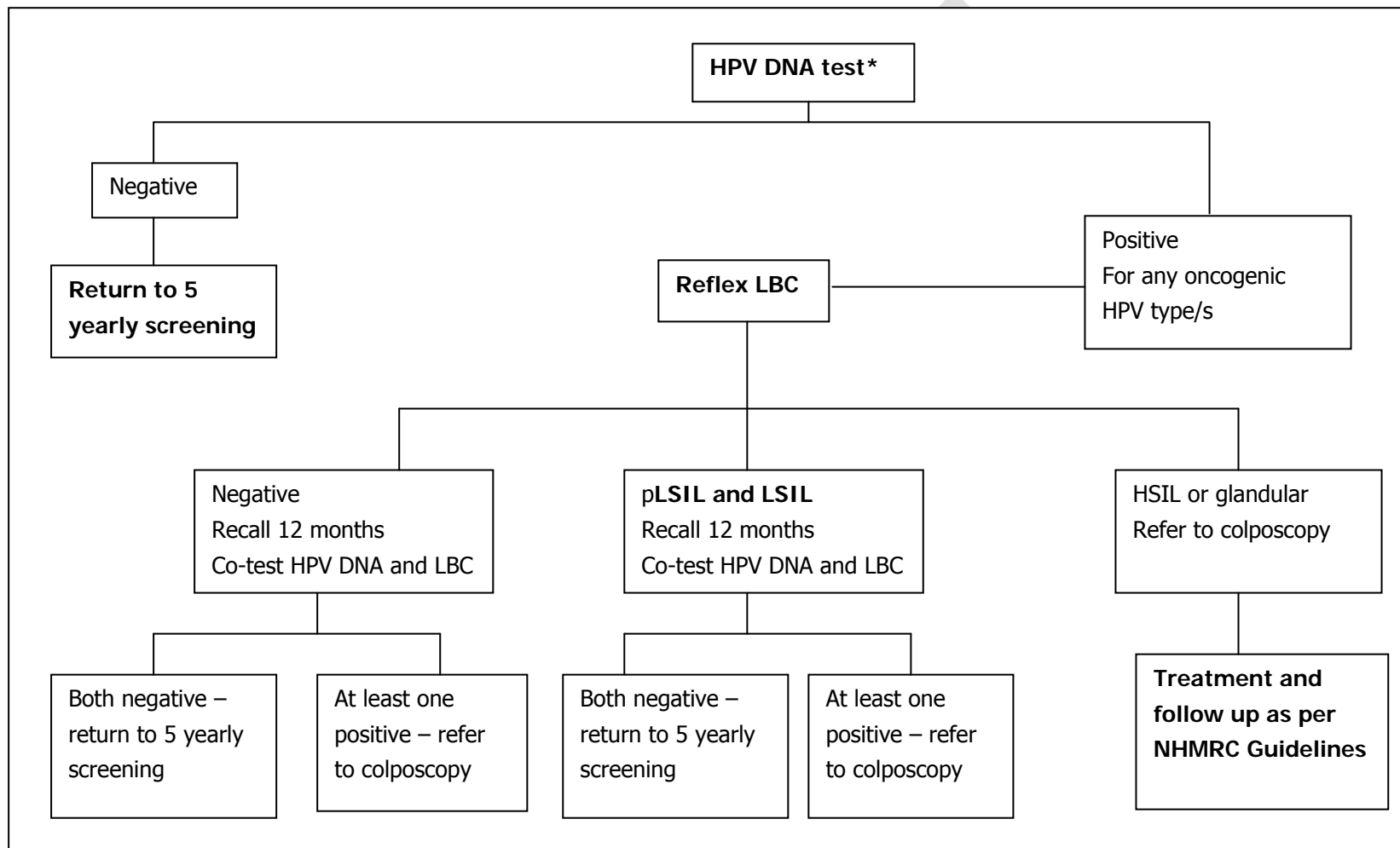
- 1) What is the comparative safety, effectiveness and cost-effectiveness of manually-read LBC or automated image analysis LBC as a co-test in the above scenario, compared with the existing protocol?
- 2) What is the comparative safety, effectiveness and cost-effectiveness of manually-read LBC or automated image analysis LBC as a reflex test to triage women with positive HPV DNA test results, compared with the existing protocol?
- 3) What is the comparative safety, effectiveness and cost-effectiveness of undertaking a colposcopy immediately in comparison to delaying the test in women who have pLSIL/LSIL cytology and a positive HPV DNA test?
- 4) What is the comparative safety, effectiveness and cost-effectiveness of including self collected samples for HPV DNA testing for underscreened³ and unscreened women, to supplement the organised screening program using practitioner collected HPV DNA samples, compared with the existing protocol?
- 5) What is the comparative safety, effectiveness and cost-effectiveness of referring women positive for HPV16/18 +/-45 using partial genotyping systems at primary screening, immediately to colposcopy, and performing cytology triage on women positive for other oncogenic types?
- 6) What is the cost-effectiveness of the pathway if an invitation/recall system was introduced, compared with the existing overdue reminder system without invitation?

² The screening interval should be no less than 5 years but a range of intervals should be explored.

³ The definition of an underscreened woman in this scenario would be any woman not screened within 12 months of her next due date for being screened.

PROPOSED ALGORITHM

Figure 4: Proposed algorithm for primary question 3



* Either HPV DNA pooled tests or HPV DNA genotyping tests could be used.

PASC considerations

PASC acknowledged that due to the scope of the cervical screening renewal program the DAP would have to be structured in a manner different to the standard format.

PASC indicated that the order of the three research questions, consideration of conventional cytology followed by LBC and then HPV DNA testing, is appropriate. PASC also indicated that the evidence base for the IARC recommendations, which serve as the suggested alternate program in the first two research questions, must be presented. PASC suggested that in order to deal with various alternative considerations scenario analyses should be used around factors such as the age ranges to be assessed, the age to exit the program, and the type of HPV DNA test to be used, as well as the comparisons suggested as 'secondary questions' described above.

The scenario analyses for primary question 3 should include consideration of the type of HPV DNA test, i.e., testing for all high-risk types as a pooled result, or technologies which allow partial genotyping for types 16/18 +/- 45 (depending on technology) and stratifying by HPV genotype. The use of tests with information on partial genotyping will imply/allow differential management strategies for women with HPV 16/18+/-45 compared to those with other oncogenic types and these should also be considered in the scenario analysis. Evidence on different screening intervals can be used to define which intervals are the most appropriate intervals to be assessed in the economic evaluation.

PASC also stated that for each research question the issues around safety should be broadly interpreted and include not only the physical effects of screening but also the psychological impact of participating in screening. These safety outcomes should be considered for different rates of cervical cancer resulting from each of the options considered.

PASC agreed that the effectiveness of HPV vaccination is not being reviewed here however the impact of HPV vaccination on cervical abnormality rates and cervical cancer into the future will be included through a dynamic modelling approach.

PASC concluded that two modelling techniques should be used and compared for all research questions: (a) a static model with current cervical abnormality rates projected into the future and (b) a dynamic model with modified cervical abnormality rates projected into the future as a consequence of the introduction of HPV vaccination.

Decision analytics

Decision analytics for the proposed structure have not been developed until finalisation of the structure following public consultation.

Attachment 1: Previous MSAC assessments for LBC

Ref 12a (2002) - Liquid based Cytology for Cervical Screening

A submission was made to the MSAC to consider the merits of replacing the conventional cytology with liquid based cytology (LBC) as the cervical screening test for possible listing on the Medicare Benefits Schedule (MBS). Cervical screening utilising LBC was intended to replace conventional cytology for detecting cancerous lesions and also pre-cancerous cells so that treatment may be initiated before the disease progresses to an inoperable stage.

Aim

The aim of the assessment was to assess the safety, effectiveness and cost-effectiveness of LBC for cervical screening.

Method

MSAC conducted a systematic review of medical literature using the Cochrane Library, Medline, PreMedline, Current Contents, Biological Abstracts, CINAHL and EMBASE databases from January 2000 - April 2002 to identify the accuracy and precision of the tests and their usefulness in terms of patient outcomes in the context of the current Australian cervical screening guidelines. Assessment of clinical effectiveness relied on five secondary studies and seven primary studies. Assessment of cost-effectiveness was based on both review of a submitted model and revision of this model on the basis that LBC was no worse than conventional cytology in detecting high-grade lesions.

Conclusions and results

Safety: No risks were associated with the test itself, although the safety issues were the same as those for conventional cytology because the method of collecting cellular material is the same for both.

Effectiveness: There was insufficient evidence to draw definitive conclusions regarding the diagnostic characteristics of LBC and conventional cytology for cervical screening. The lack of high quality evidence on the performance of LBC did not permit evaluation of whether it was equal or superior in effectiveness to conventional cytology. The assessment concluded that further high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, would be crucial in allowing a valid and reliable judgement concerning the sensitivity and specificity of LBC.

Cost-effectiveness: A decision analytic model indicated that LBC was associated with greater costs per woman than conventional cytology. Since there was insufficient evidence to support a claim that LBC is superior to conventional cytology in detecting high-grade lesions or invasive cancer, it followed that there is no evidence to suggest that LBC would be cost-effective at the proposed price.

Recommendations

MSAC advised that there was insufficient evidence to support public funding of liquid based cytology for cervical screening at the time of the assessment.

1122 (2009) - Automation-Assisted and Liquid-Based Cytology for Cervical Cancer Screening

Aim

The primary research question was:

- What is the safety, effectiveness and cost-effectiveness of liquid-based cytology (LBC) using automated image analysis systems in comparison to manual reading of conventionally prepared Pap smear cytology samples for the screening and diagnosis of cervical cancer?

The following secondary research questions were also addressed in terms of the safety, effectiveness and cost-effectiveness of;

- LBC compared to conventionally prepared Pap smear cytology samples when manual reading of slides is used?
- automated image analysis systems in comparison to manual reading of conventionally prepared Pap smear cytology samples?
- LBC using automated image analysis systems compared to manual reading of LBC?

Methods

A systematic review was undertaken of the medical literature published since the last MSAC report in 2002 - up to 6 February 2008 - on the evidence for automation-assisted and liquid-based cytology for cervical cancer screening.

Results and conclusions

Safety The assessment reported noted that LBC with manual or automation-assisted slide reading uses the same procedure for collecting cervical cell samples as conventional Pap cytology tests and is considered a safe procedure.

Effectiveness No studies assessed the impact of LBC with manual or automated slide reading on the incidence of invasive cervical cancer or consequent mortality rates compared to conventional cytology. The review therefore relies on evidence about the accuracy of manual or automated LBC for detecting precancerous cervical lesions to draw conclusions about its relative effectiveness. The report concluded that manual LBC compared to conventional cytology provides no statistically significant increase in sensitivity or specificity; provides no statistically significant difference in sensitivity (HSIL, LSIL or pLSIL thresholds) or specificity (HSIL or LSIL thresholds) for the detection of CIN 2+; and reduces the specificity for the detection of CIN 2+ at a test threshold of pLSIL. Automated LBC detects more CIN 2+ lesions compared to conventional cytology, but results from one trial raises

uncertainty about whether this difference is attributable to LBC alone, to the automation-assisted reading system or a combination of both. Both manual and automated LBC classify more slides as positive for low-grade lesions; both reduce the rate of unsatisfactory smears. Automated LBC also reduces slide processing time.

Economic considerations A modelled analysis based on favourable assumptions regarding test characteristics found that automated LBC (ThinPrep Imager) would be associated with a cost of \$194,835 per LYS. Manual LBC was associated with a cost of \$126,315 per LYS to \$385,982 per LYS depending on the level of reimbursement. The analysis predicted automated LBC would prevent 68 cervical cancer cases and 19 deaths due to cervical cancer annually, and that manual LBC would prevent 23 cervical cancer cases and 6 deaths due to cervical cancer annually. Both would also result in additional follow-up procedures. Each cancer case averted with automated LBC would require an additional 566 cytology tests, 159 colposcopies, 76 biopsies and 26 treatments for CIN 2/3. Each cancer case averted with manual LBC would require an additional 990 cytology tests, 295 colposcopies, 142 biopsies and 32 treatments for CIN 2/3. The findings are sensitive to assumed relative test accuracy, differences in the unsatisfactory smear rate, assumptions about disease natural history (particularly for high-grade regression and progression), the recommended screening interval and the cost of the new technology. The results presented were based on the current screening program in Australia without taking into account potential changes resulting from HPV vaccination.

Recommendations

MSAC's advice was, with respect to LBC, that in comparison to conventional cytology, LBC is safe, is at least as effective, but is not cost effective at the price requested and advised that LBC should not be supported for public funding.

With respect to automated (computerised) testing of LBC, that in comparison to conventional cytology, automated LBC testing is safe, is at least as effective, but is not cost effective at the price requested. MSAC advised that automated testing of LBC specimens should not be supported for public funding.

Attachment 2: Previous MSAC assessments for HPV DNA testing

Ref 12b (2002) - Human Papillomavirus Testing in Women with Cytological Prediction of Low-grade Abnormality

Aim

To assess the safety, effectiveness and cost-effectiveness of HPV testing in women with cytological prediction of low-grade abnormality.

The report presented an evaluation of the clinical effectiveness and cost-effectiveness of the HC-II HPV DNA (HC-II) test in women with cytological prediction of low-grade abnormality. It integrated submissions made to the MSAC from the technology manufacturer and a request made to the MSAC from within the Commonwealth Department of Health and Ageing.

A submission was made to the MSAC to consider the merits of adjunctive HPV testing as an aid for diagnosing the presence of high-risk HPV subtypes in women with screen-detected low-grade abnormality for possible listing on the Medicare Benefits Schedule (MBS).

Method

MSAC conducted a systematic review of medical literature using the Cochrane Library, Medline, PreMedline, Current Contents, Biological Abstracts, CINAHL and EMBASE databases from January 1999 - April 2002 to identify the accuracy of the test and its usefulness in the context of the current Australian cervical screening guidelines. Assessment of clinical effectiveness relied on one secondary study and seven primary studies. Assessment of cost-effectiveness was based on both review of a submitted model and a decision analytic model simulating the cost-effectiveness of HPV testing in women with cytological prediction of low-grade abnormality.

Conclusions and Results

Safety No risks were associated with the test itself. Safety issues were the same as those for conventional cytology because the method of collecting cellular material is the same.

Effectiveness A systematic review concluded that HPV testing was more sensitive but less specific than cytology, although current evidence would not support widespread implementation. Although it was inappropriate to calculate an overall summary statistic as primary studies reported varying positive thresholds for HPV testing, pooling four of seven studies revealed a sensitivity of 92% (95% CI: 87%, 97%) and specificity of 54% (95% CI: 50%, 57%) in detecting lesions that were moderately dysplastic or worse. It was noted that these results should be interpreted with caution as studies failed to meet all validity criteria, which may result in non-appraisable bias. The assessment concluded that additional high quality studies using an acceptable reference standard, such as histological confirmation of cytology results, would be useful in allowing a valid and reliable judgement of the sensitivity and specificity of HPV testing in this population.

Cost-effectiveness A decision analytic model indicated that HPV testing was both more expensive and less effective in detecting high-grade lesions than the management plan currently recommended by the NHMRC, but the model was particularly sensitive to the estimated prevalence of high-grade lesions in women.

Recommendations

MSAC advice was that there was currently insufficient evidence to support public funding at the time for the use of the HPV test for triaging of women with equivocal cervical screening results.

Ref 12d (2003) - Human Papillomavirus Testing for Cervical Cancer

Aim

The aim of the assessment was to assess the safety, effectiveness and cost-effectiveness of human papillomavirus testing by the Hybrid Capture II (HC-II) test for cervical screening as either a stand-alone screening test or combined with screening by cytology. The report reviewed the detection of high-risk HPV subtypes by the HC-II test for routine cervical screening either as a stand-alone screening test or as an adjunct to either conventional cytology or liquid-based smear.

Method

MSAC conducted a systematic review of medical literature using the Cochrane Library, Medline, PreMedline, Current Contents, Biological Abstracts, CINAHL and EMBASE databases from January 1998 - October 2002 to identify the accuracy and precision of the tests and their usefulness in terms of patient outcomes in the context of the current Australian cervical screening guidelines. Assessment of clinical effectiveness relied on two primary studies, while assessment of cost-effectiveness was based on review of a submitted economic model.

Conclusions and results

Safety No risks were associated with the test itself, although the safety issues were the same as those for conventional cytology because the method of collecting cellular material is the same for both.

Effectiveness There was insufficient evidence that HPV testing is effective in detecting high grade cervical lesions when used as either a stand-alone screening test or combined with screening by cytology.

Cost-effectiveness Due to insufficient evidence of clinical effectiveness, an economic evaluation could not be performed.

Recommendations

MSAC advised that there was insufficient evidence to support public funding of HPV testing as a stand-alone screening test or as an adjunct to cervical cytology screening.

Further research

The assessment noted that at the time, three trials were underway, enrolling more than 43,000 women with results expected over the next three years: HART (UK), ARTISTIC (UK) and CCaST (Canada).

Ref 39 (2009) - Human Papillomavirus Triage Test for Women with Possible or Definite Low-Grade Squamous Intraepithelial Lesions

Aim: The aim of this assessment was to assess the safety, effectiveness and cost-effectiveness of the Hybrid Capture II (HC-II) human papillomavirus (HPV) triage test for asymptomatic women with a routine screening cervical cytology test finding of possible or definite low-grade squamous intra-epithelial lesions (LSIL) when testing is conducted either at the time of the index cytology result; or with repeat cytology 12 months after the index cytology test, compared with the standard strategy of repeating cervical cytology annually for 2 years. In addition, assessment of the HPV triage test was undertaken for subgroups of women: with an index cytology finding of definite LSIL (dLSIL) only; possible LSIL (pLSIL) only; aged ≥ 23 years; and aged ≥ 30 years.

Methods

A systematic review was undertaken of the medical literature published since the last MSAC report in 2002 - up to 6 February 2008 - to report on the evidence addressing the research questions. This evidence was used to identify 18 potential HPV triage strategies for further assessment. A comprehensive model of cervical screening, diagnosis and treatment was developed to estimate and compare the incremental effectiveness and cost-effectiveness of adopting each of these strategies in Australia.

Results and conclusions

Safety The assessment concluded that the HC-II HPV test is a technically safe procedure.

Effectiveness No published clinical studies comparing the impact of the HPV triage test on invasive cervical cancer incidence or mortality rates compared with the current standard strategy of repeat cytology testing of women with an index cytology finding of pLSIL or dLSIL were identified. Comparative accuracy studies provided strong evidence that an immediate HC-II HPV triage test is a more sensitive test than a single repeat cytology test for detecting cervical intraepithelial neoplasia (CIN) 2+ lesions in women with pLSIL, and has similar specificity. There was also strong evidence that an immediate HC-II HPV triage test is no more sensitive than a single repeat cytology test for detecting CIN 2+ lesions in women with dLSIL, and has lower specificity, but colposcopy referral rates may be favourable compared with a strategy of two annual repeat cytology tests in this patient group. Restricting the HPV triage test to older age groups is associated with a higher specificity and lower colposcopy referral rate and a corresponding smaller gain in sensitivity compared with its use in all age groups. No published clinical studies comparing the accuracy of performing the HC-II HPV test with repeat cytology at the 12-month follow-up visit with the current strategy were identified.

Economic considerations The modelled analysis predicted that, compared with current practice, a strategy of performing the HPV triage test for women aged 30+ years produces an incremental cost-effectiveness ratio (ICER) of \$75,739 per life year saved (LYS) if conventional cytology is used with co-collection for HPV testing; or \$83,496 per LYS using manual liquid based cytology (LBC) (at an incremental price of \$2.40 compared with conventional cytology) with reflex HPV testing; or \$170,209 per LYS using automated LBC with reflex HPV testing. When compared with current practice using conventional cytology, the most cost-effective options were strategies involving immediate triage either with conventional cytology and co-collection or with reflex manual LBC testing (at an incremental price of \$2.40 compared with conventional cytology). The evaluation found that performing immediate HPV triage is substantially more cost-effective than delaying triage testing until a 12-month follow-up visit, for all types of cytology (conventional with co-collection, manual LBC and AutoLBC). The ICER estimates were most sensitive to assumptions concerning the cost of the HPV test and cytology tests including the cost of co-collection, the HPV test characteristics, the discount rate, the recommended screening interval, and the likelihood that CIN 3 lesions will progress to cancer. The results presented were based on the current screening program in Australia without taking into account potential changes resulting from HPV vaccination.

Recommendation

MSAC's advice was that HPV triage testing in cervical cancer was not cost effective in the Australian setting at the current price of HPV testing and did not support public funding.

Attachment 3: Consideration of other technologies

Ref 12c (2003) - Computer-assisted Image Analysis for Cervical Screening

Aim

To assess the safety, effectiveness and cost-effectiveness of computer-assisted image analysis for cervical screening cytology compared with manual processing. The comparator for computer-assisted image analysis was conventional manual screening in which trained laboratory personnel examine the slides using light microscopy.

Method

MSAC conducted a systematic review of medical literature using the Cochrane Library, Medline, PreMedline, Current Contents, Biological Abstracts, CINAHL and EMBASE databases from January 1966 to September 2002 to identify the accuracy and precision of the tests and their usefulness in terms of patient outcomes. This report adopted the criteria for assessment of validity of evidence recommended by the Cochrane Methods Working Group on Systematic Review of Screening and Diagnostic Tests.

Conclusions and results

Safety Computer-assisted image analysis is conducted in the laboratory on the same slides as conventional cervical cytology. The safety issues with this technology were the same as those for the cytological assessment methods in current use.

Effectiveness There was insufficient evidence to assess whether computer-assisted image analysis is as effective as manual processing for cervical screening cytology.

Cost-effectiveness Due to insufficient evidence of clinical effectiveness, an economic evaluation could not be performed.

Recommendations

MSAC advised that there was insufficient evidence to support public funding of computer-assisted image analysis for cervical screening at this time.

Attachment 4: NHMRC Guidelines for follow-up of abnormalities

Table A4.1: Summary of NHMRC Guidelines for the management of asymptomatic women with screen detected abnormalities

Guideline	Evidence
Management of women with unsatisfactory smears	
<p><u>Unsatisfactory Pap test reports</u> A woman with an unsatisfactory Pap test report should have a repeat smear in 6–12 weeks, with correction, when possible, of the problem that caused the unsatisfactory smear.</p>	Consensus
Management of low-grade squamous abnormalities	
<p><u>Human papilloma virus (HPV) testing</u> There is insufficient evidence to support the use of HPV testing in the triage of low-grade squamous intraepithelial lesions.</p>	MSAC 2002
<p><u>Index Pap test report of low-grade squamous intraepithelial lesions (LSIL)</u> A woman with a Pap test report of LSIL should be managed in the same way irrespective of whether the abnormality is regarded as possible or definite and should be recommended for a repeat Pap test in 12 months.</p>	Australian registry data; Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)
<p><u>Index Pap test reports of LSIL in women aged 30+ years</u> A woman aged 30 years or more with a Pap test report of LSIL, without a history of negative smears in the preceding two to three years, should be offered either immediate colposcopy or a repeat Pap smear within six months.</p>	Australian registry data
<p><u>Twelve-month repeat Pap test after index test results of LSIL</u> If the 12-month repeat Pap test is reported as showing high-grade changes (definite or possible), the woman should be referred for colposcopic assessment. Any woman whose repeat Pap test at 12 months is again reported as showing changes suggestive of LSIL (whether possible or definite), should be referred for colposcopic assessment. If the 12-month repeat Pap test is reported as normal, the woman should have a further repeat Pap test in 12 months (ie 24 months after the index smear).</p>	Level IV (Schoolland et al 1998, Sparkes et al 2000, Performance Standards 2003) Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)
<p><u>Fluctuating repeat Pap test results</u> Referral for colposcopy should be considered for a woman if she has two LSIL/possible LSIL reports (at least 12 months apart) within a 3-year timeframe, regardless of intervening normal cytology reports.</p>	Consensus
<p><u>Colposcopic assessment of women with Pap test reports of LSIL</u> If, at colposcopy, a high-grade lesion is seen or suspected, targeted biopsy should be performed for histological confirmation before definitive therapy. If the colposcopic assessment is normal, the woman should be referred back for annual cytological surveillance until two normal smears are obtained, and then resume routine screening according to the recommendation for the average population. If the colposcopic assessment is satisfactory and a low-grade lesion is suspected, target biopsy can be performed to confirm this diagnosis. Treatment of histologically confirmed low-grade squamous lesions is not recommended, as such lesions are considered to be an expression of a productive HPV infection. Histologically confirmed low-grade squamous abnormalities can be safely managed by repeat cytology at 12 and 24 months. If both smears are negative, it is recommended that the woman return to screenings at the intervals recommended for the average woman.</p>	Consensus (RANZCOG 2001)

Guideline	Evidence
<p>If either repeat smear shows possible or definite LSIL, the woman should be advised to continue having annual smears until at least two are negative, at which time she can return to routine screening.</p> <p>If the colposcopic assessment is unsatisfactory, consideration should be given to repeating the Pap test in 6–12 months. In asymptomatic women and in the absence of any cytologic, colposcopic or histologic suggestion of high-grade disease, further diagnostic procedures, such as cone biopsy or loop excision, are not indicated.</p>	
Management of high-grade squamous abnormalities	
<p><u>Referral of women with Pap test reports of possible high-grade squamous lesions</u> A woman with a Pap test report of possible high-grade squamous lesion should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.</p>	Level IV (Schoolland et al 1998, Sparkes et al 2000, VCCR 2002)
<p><u>Referral of women with Pap test reports of high-grade squamous intraepithelial lesions (HSIL)</u> A woman with a Pap test report of HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.</p>	Level IV (VCCR 2002, Sparkes et al 2000)
<p><u>Referral of women with Pap test reports of HSIL with additional features suggestive of an invasive component</u> A woman with a Pap test report of HSIL, with additional features suggestive of an invasive component, should be referred to a gynaecologist with expertise in colposcopic evaluation of suspected gynaecological malignancies or to a gynaecological oncologist, ideally within two weeks.</p>	Consensus
<p><u>Referral of women with Pap test reports of SCC</u> A woman with a Pap test report of SCC should be referred to a gynaecological oncologist or to a gynaecological oncology unit for urgent evaluation, ideally within two weeks.</p>	Consensus
<p><u>Histological confirmation</u> Histological confirmation of a high-grade lesion is required before definitive treatment is undertaken. 'See and treat' is not recommended.</p>	Consensus
<p><u>Treatment of a high-grade squamous intraepithelial abnormality</u> Women with a histological diagnosis of CIN 2 or CIN 3 should be treated in order to reduce the risk of developing invasive cervical carcinoma.</p>	Level III-2 (Östör 1993b)
<p><u>Fertility-sparing treatments</u> Local ablative or excisional treatments should destroy or remove tissue to a depth of at least 7 mm. There is no clearly superior method of fertility-sparing treatment for CIN 2 and 3.</p>	Level IV (Burke 1982, Jordan et al 1985) Level I (Martin-Hirsch et al 2000)
<p><u>Ablative therapy</u> Ablative therapy may be considered, provided:</p> <ol style="list-style-type: none"> 1. The cervix has been assessed by an experienced colposcopist. 2. A targeted biopsy has confirmed the diagnosis. 3. There is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy. 4. The entire cervical transformation zone has been visualised. 5. There is no evidence of a glandular lesion on cytology or biopsy. 	Consensus
<p><u>Cryotherapy for treatment of CIN 3</u> It is advisable that women with CIN 3 are not treated with cryotherapy.</p>	Level IV (Anderson and Husth 1992)
<p><u>Loop electro-excisional procedure (LEEP)</u> Excess diathermy artefact should be avoided when using LEEPs in order to allow comprehensive pathological examination, including margin status.</p>	Consensus
<p><u>Cone biopsy</u> Cone biopsy may be necessary to treat women with high-grade squamous lesions and absolute indications that include:</p> <ol style="list-style-type: none"> 1. failure to visualise the upper limit of the cervical transformation zone in a woman with a high-grade squamous abnormality on her referral cervical smear (ie unsatisfactory colposcopy) 	Consensus

Guideline	Evidence
<p>2. suspicion of an early invasive cancer on cytology, biopsy or colposcopic assessment</p> <p>3. the suspected presence of an additional significant glandular abnormality (ie adenocarcinoma in situ) on cytology or biopsy (ie a mixed lesion). Careful attention should be paid to tailoring treatment to the individual woman, taking into account the size, extent, situation and severity of the lesion.</p>	
<p><u>Management of women previously treated for HSIL</u></p> <p>A woman previously treated for HSIL requires a colposcopy and cervical cytology at 4–6 months after treatment. Cervical cytology and HPV typing should then be carried out at 12 months after treatment and annually thereafter until the woman has tested negative by both tests on two consecutive occasions. The woman should then be screened according to the recommendation for the average population. A woman already undergoing annual cytological review for follow-up of a previously treated HSIL, as advised by the previous NHMRC guidelines (1994), may be offered HPV testing as described above. Once she has tested negative by both cytology and HPV typing on two consecutive occasions, she should be screened according to the recommendation for the average population.</p>	<p>Level IV (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004)</p>
<p><u>Management of cervical glandular abnormalities</u></p> <p><u>Referral of women with Pap test reports of adenocarcinoma</u></p> <p>A woman with a Pap test report of adenocarcinoma of endometrial origin should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist. A woman with a cytological prediction of adenocarcinoma of either endocervical, extrauterine or unspecified origin should be referred to a gynaecological oncologist or a gynaecological oncology unit.</p>	<p>Level III-3 (Mitchell et al 1993)</p> <p>Consensus</p>
<p><u>Referral of women with Pap test reports of endocervical adenocarcinoma in situ (AIS)</u></p> <p>A woman with a Pap test report of endocervical AIS should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist</p>	<p>Australian registry data</p>
<p><u>Referral of women with Pap test reports of possible high-grade glandular lesions</u></p> <p>A woman with a Pap test report of possible high-grade glandular lesions should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.</p>	<p>Australian registry data</p>
<p><u>Referral of women with Pap test reports of atypical glandular or endocervical cells of undetermined significance</u></p> <p>A woman with a Pap test report of atypical glandular or endocervical cells of undetermined significance should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies.</p>	<p>Australian registry data</p>
<p><u>Colposcopic assessment of glandular lesions</u></p> <p>Colposcopic assessment is mandatory in the presence of a cervical cytology suggesting a glandular lesion.</p>	<p>Consensus</p>
<p><u>Cone biopsy for the assessment of glandular lesions</u></p> <p>Cold-knife cone biopsy should be considered the 'gold standard' for the assessment of glandular lesions</p>	<p>Consensus</p>
<p><u>Referral of women with adenocarcinoma on cone or punch biopsy</u></p> <p>Women found to have invasive adenocarcinoma on cone or punch biopsy should be referred to a gynaecological oncologist or a gynaecological oncology unit for subsequent management.</p>	<p>Consensus</p>
<p><u>Management of women with a Pap test report of AIS</u></p> <p>If invasive carcinoma is not identified at colposcopic assessment, a cone biopsy should be undertaken. Hysterectomy should not be undertaken without prior cone biopsy to exclude invasive carcinoma.</p>	<p>Consensus</p>
<p><u>Management of women with AIS</u></p> <p>The management of women diagnosed with AIS on cone biopsy will be dependent upon the age and fertility requirements of the women and the status of excision margins. Hysterectomy is recommended for women who have completed childbearing because of the difficulties of reliable cytological follow-up, a high recurrence rate</p>	<p>Level IV (Cullimore et al 1992, Hopkins et al 1988, Muntz et al 1992, Im et al 1995, Poynor et al 1995, Denehy et al 1997, Widrich et al 1996, Wolf et al 1996, Azodi et</p>

Guideline	Evidence
and the reported multifocality of the disease.	al 1999, Hopkins 2000, Souter et al 2001, Anderson and Nielson 2002, Kennedy and Biscotti 2002, Shin et al 2002)
Special clinical circumstances	
<p><u>Evaluation of an abnormal Pap test during pregnancy</u> Women with low-grade cytologic lesions should be managed in the same way as for women with low-grade squamous abnormalities, with a repeat smear after 12 months.</p> <p>Women with high-grade lesions should be referred for colposcopic evaluation.</p>	<p>Level IV (Coppola et al 1997, Jain et al 1997, Woodrow et al 1998, Nguyen et al 2000)</p> <p>Level IV (Coppola et al 1997, Woodrow et al 1998, Nguyen et al 2000, Palle et al 2000)</p>
<p><u>Colposcopy during pregnancy</u> The main aim of colposcopy in the pregnant woman is to exclude the presence of invasive cancer and to reassure the woman that her pregnancy will not be affected by the presence of an abnormal Pap test.</p> <p>Biopsy of the cervix is usually unnecessary in pregnancy, unless invasion is suspected colposcopically.</p>	<p>Level IV (Woodrow et al 1998)</p> <p>Level IV (Woodrow et al 1998, Palle et al 2000)</p>
<p><u>Treatment of a high-grade lesion during pregnancy</u> Definitive treatment of a high-grade lesion, with the exception of invasive cancer, may be deferred safely until after the pregnancy.</p>	<p>Level IV Guerra et al (1998), Economos et al (1993)</p>
<p><u>Immunosuppressed women</u> If an immunosuppressed woman has a screen-detected abnormality she should be referred for colposcopy, even if the lesion is low-grade, as cytological surveillance alone may be inadequate.</p> <p>Assessment and treatment should be by an experienced colposcopist.</p> <p>The whole of the lower genital tract will need evaluation as the same risk factors apply for cervical, vaginal, and vulval and perianal lesions.</p> <p>Treatment of the cervix should be by excisional methods.</p> <p>Follow-up after treatment should include colposcopy as well as cytology.</p> <p>Follow-up should be annual and indefinite.</p>	<p>Level I/II (Sillman et al 1997, Spitzer 1999)</p> <p>Level III-1 (Petry et al 1994)</p> <p>Level III-1 (Petry et al 1994)</p> <p>Level I/II (Spitzer 1999)</p> <p>Level III-2 (Cordiner et al 1980)</p> <p>Level III-2 (Cordiner et al 1980)</p>
<p><u>Postmenopausal women with normal endometrial cells</u> Normal endometrial cells occurring in the Pap smear of an asymptomatic postmenopausal woman should not be reported.</p> <p>A symptomatic postmenopausal woman requires investigation irrespective of her Pap test status.</p>	<p>Level III-2 (Gondos and King 1977, Gomez-Fernandez et al 2000, Ashfaq et al 2001, Montz 2001, Chang et al 2001, Brogi et al 2002)</p> <p>Level III-2 (RANZCOG 2002)</p>
<p><u>Women exposed to diethylstilboestrol (DES) in utero</u> DES-exposed women should be offered annual cytological screening and colposcopic examination of both the cervix and vagina.</p> <p>Screening should begin any time at the woman's request and continue indefinitely. A balanced perspective should be maintained.</p> <p>DES-exposed women who have a screen-detected abnormality should be managed in a specialist centre by an experienced colposcopist.</p>	<p>Level IV (Hacker 2000, RCOG 2002)</p> <p>Level IV (Hacker 2000, RCOG 2002)</p> <p>Level IV (Hacker 2000, RCOG 2002)</p>

Attachment 5: Summary of screening programs

Table A5.1: Summary of screening programs

Country	Estimated Incidence 2008 [#]	Estimated Mortality 2008 [#]	Population	Frequency of testing			HPV vaccine recommendation
				Conventional cytology	Liquid-based cytology	HPV DNA test	
Australia ^a	4.9	1.4	All woman sexually active between 18 and 20 years of age, or 1-2 years after first having sexual intercourse, whichever is later	Every 2 years (if no symptoms or history suggestive of cervical pathology)	-	-	Females aged 12-13 ^b
			≥70 years of age and two normal test results within the last five years.	Screening may cease unless requested	-	-	
			≥70 years of age and never been tested	Screened	-	-	
United States of America ^c	5.7	1.7	Women age 21-65 years	Screening with cytology (Pap smear) every 3 years	-	-	Girls aged 11 to 12 ^d
			Women aged 30 years to 65 years	Screen with cytology every 3 years or co-testing (cytology/HPV every 5 years)	-	-	
Canada ^e	6.6	1.9	≥18 years of age or sexually active	Every 1 year	-	Available but not part of screening program	Primarily recommended in females between 9 and 13 years of age but also in females between 14 and 26 of age ^f
			18-69 years of age or sexually active and first two results normal	Every 3 years	-		
			≥70 years of age and at least two normal results and no cervical abnormalities for nine years	Screening stoped	-		
			Abnormality detected	Every 6 months 2 years	-		
			Women who have had total hysterectomy, unless surgery was treatment for cervical cancer or pre-cancer	Screening stoped	-		
United Kingdom ^g	7.2	2.0	Aged between 25-49	-	Every 3 years	HPV triage only (performed in women with a cervical screening test result of borderline changes or mild dyskaryosis)	Females aged 12-13 ^h
			Aged between 50-64	-	Every 5 years		
			Aged ≥65 years	-	Only those who have not been screened since age 50 or have		

Country	Estimated Incidence 2008 [#]	Estimated Mortality 2008 [#]	Population	Frequency of testing			HPV vaccine recommendation
				Conventional cytology	Liquid-based cytology	HPV DNA test	
Austria ⁱ	5.7	2.3	≥18	Every 1 year*	-	-	19-15 years of age ^j
Belgium ⁱ	8.4	2.7	25-64 years of age	Every 3 years*	-	-	10-13 years of age ^j
Bulgaria ⁱ	21.9	6.5	31-65 years of age	Every 2 years*	-	-	None ^j
Czech Republic ⁱ	14.0	3.9	25-69 years of age	Every 1 year*	-	-	None ^j
Denmark ^{i,l}	12.1	2.5	23-59 years of age	Every 3 years	-	-	12 years of age ^j
			>45 or 50 (some counties only)	Every 5 years	-	-	
Estonia ^{i,k}	15.9	6.2	30-59 years of age	Every 5 years, after one negative smear	-	-	None ^j
Finland ^{i,l}	4.5	1.2	30-60 years of age	Every 5 years	-	-	None ^j
France ⁱ	7.1	1.8	25-65 years of age	Every 3 years*	-	-	14 years of age ^j
Germany ⁱ	6.9	2.3	≥20	Every 1 year*	-	-	12-17 years of age ^j
Greece ⁱ	4.1	1.6	≥20	Every 1 year*	-	-	12-15 years of age ^j
Hungary ^{i,l}	16.6	5.6	25-65 years of age	Every 3 years, after one negative smear	-	-	None ^j
Iceland ⁱ	8.4	0.8	20-69 years of age	Every 2 years	-	-	12 years of age ^j
Ireland ⁱ	10.9	3.3	25-60 years of age	Every 3 years*	-	-	12 years of age ^j
				Every 5 years*	-	-	
Italy ⁱ	6.7	1.5	25-64 years of age	Every 3 years*	-	-	12 years of age ^j
Latvia ⁱ	12.4	7.3	20-70 years of age	Every 3 years*	-	-	None ^j
Lithuania ^{i,l}	21.0	8.3	30-60 years of age	Every 3 years (also reported as every 5 years)	-	-	None ^j
Luxembourg ^{i,l}	6.3	1.9	≥15 years of age	Every 1 year	-	-	11-12 years of age ^j
Netherlands ^{i,l}	6.8	1.9	30-60 years of age	Every 5 years	-	-	12 years of age ^j
Norway ⁱ	9.4	2.3	25-69 years of age	Every 3 years	-	-	12 years of age ^j
Poland ⁱ	11.6	5.8	25-59 years of age	Every 3 years*	-	-	None ^j
Portugal ⁱ	12.2	3.6	25-64 years of age	Every 3 years*	-	-	13 years of age ^j
Romania ⁱ	23.9	11.8	25-65 years of age	Every 5 years*	-	-	10-11 years of age ^j
Slovak Republic ⁱ	15.8	4.8	≥18 years of age	Every 1 year*	-	-	None ^j
Slovenia ^{i,l}	11.1	2.8	20-64 years of age	Every 3 years	-	-	None ^j
Spain ^{i,l}	6.3	1.9	20-34 years of age	Every 3 years (initially	-	-	11-14 years of age ^j

Country	Estimated Incidence 2008 [#]	Estimated Mortality 2008 [#]	Population	Frequency of testing			HPV vaccine recommendation
				Conventional cytology	Liquid-based cytology	HPV DNA test	
				two smears 1 year apart)			
			35-64 years of age	Every 5 years	-	-	
Sweden ^{i, l}	7.8	1.9	23-50 years of age	Every 3 years	-	-	11-12 years of age ^j
			51-60 years of age	Every 5 years	-	-	
New Zealand ^m	5.5	1.6	Women aged 20 to 70 years of age	Every three years		Women over 30 years with ASC-US or LSIL cytology	Girls aged 12 to 18 ⁿ

[#] GLOBOCAN 2008 (IARC) accessed at <http://globocan.iarc.fr/factsheet.asp> on 10 May 2012

*Details of diagnostic method not provided

HPV = human papillomavirus.

^a Australian Government, Department of Health and Ageing. National Cervical Screening Program. Last accessed 29 February 2012:

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^b Australian Government, Department of Health and Ageing. National Immunization Program Schedule, Last accessed 29 February 2012:

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^c Moyer, V. Screening for Cervical Cancer: US Preventative Services Task Force Recommendation Statement. *Annals of Internal Medicine*. June 2012.

^d Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin*. 2007;57:7-28.

^e Public Health Agency of Canada. Last accessed 28 February 2012: <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/diseases-maladies/cervical-uterus-eng.php>

^f An Advisory Committee Statement (ACS), National Advisory Committee on Immunization (NACCI). *Update on Human Papillomavirus (HPV) Vaccines*. Canada Communicable Disease Report. 2012 (38)

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^h National Health Service. Vaccinations. Last accessed 29 February 2012: <http://www.nhs.uk/Planners/vaccinations/Pages/Teenagershub.aspx>

ⁱ European Commission. Cancer screening in the European Union, Report on the implementation of the Council Recommendation on cancer screening. 2008

^j European Cervical Cancer Association. HPV Vaccination Across Europe. 2009

^k Veerus P, Arbyn M, Amati C, Paolo B. Impact of implementing a nationwide cervical cancer screening program on female population coverage by Pap-tests in Estonia. *Tumori*. 2010; 96(4): 524-8.

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^m New Zealand Government. New Zealand Screening Unit. National Cervical Screening Programme. Last accessed 12 May 2012: www.nsu.govt.nz/current-nsu-programmes/national-cervical-screening-programme.aspx

ⁿ New Zealand HPV Project. Last accessed 12 May 2012: www.hpv.org.nz/patient/HPV_vaccine.htm

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