



Australian Government

Medical Services Advisory Committee

MSAC Outcomes

Application No. 1276 – Renewal of the National Cervical Screening Program

Sponsor/Applicant/s: Standing Committee on Screening

Date of MSAC consideration: MSAC 61st Meeting, 3-4 April 2014

1. Purpose of application

The Standing Committee on Screening of the Australian Health Ministers' Advisory Council (AHMAC), supported by the Australian Government's Department of Health is undertaking a Renewal of the National Cervical Screening Program (NCSP). The aim of the NCSP Renewal is to ensure that all Australian women, human papillomavirus (HPV) vaccinated and unvaccinated, have access to a cervical screening program that is safe, acceptable, effective, efficient and based on current evidence. An application requesting review of the MBS listing of cervical cytology for screening asymptomatic women was received from the Standing Committee on Screening by the Department of Health in January 2012.

The Medical Services Advisory Committee (MSAC) is being asked to provide advice on the safety, effectiveness and cost effectiveness of a potential new cervical screening pathway for the NCSP which will inform policy and MBS changes. This application is multi-tiered, allowing for consideration of screening tests, screening intervals, the target age range and screening pathways; the impact of HPV vaccination and the cost-effectiveness of different screening tests and pathways.

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.

2. Background

Cervical cancer affects the cells of the 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, 65.4% of cervical cancers were squamous cell carcinoma and 25.6% were adenocarcinoma, with adenosquamous (3.3%) and other cervical cancers (5.8%) making up the remainder (AIHW 2013a).

Cervical cancer is the 12th most common cancer affecting Australian women (excluding basal and squamous cell carcinoma of the skin). In 2009, for which the latest data is available, there were 8.9 new cases of cervical cancer and 2.0 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 10.6 per 100,000 women in the period 2004 to 2008 (AIHW 2013a)..

The Australian Government has a two pronged approach to the prevention and early detection of cervical cancer: the Human Papillomavirus (HPV) Vaccination Program and the NCSP. Since January 2007, the Australian Government has funded the cervical cancer vaccine, for 12 to 13 year old girls. In 2013 boys also commenced HPV vaccination. The HPV Vaccination Program aims to prevent about 70 per cent of all HPV infections that are known to cause cervical cancer.

The NCSP Renewal seeks to ensure that all Australian women continue to have access to a screening program that is based on current evidence and that is safe, acceptable, effective and efficient.

The objectives of the Renewal are to:

1. assess the evidence for screening tests and pathways, the screening interval, age range and commencement for both vaccinated and non-vaccinated women;
2. determine a cost-effective screening pathway and program model;
3. investigate options for improved national data collection systems and registry functions to enable policy, planning, service delivery and quality management; and
4. assess the feasibility and acceptability of the renewed program.

The first two objectives (phase 1) outlined above are being undertaken through the MSAC process to identify a renewed NCSP screening pathway that is safe, effective and cost-effective. Objectives three and four (phase 2) will be considered by the Standing Committee on Screening of the Australian Health Ministers' Advisory Council.

Stakeholder involvement

The Renewal has been guided by the Renewal Steering Committee (RSC) on behalf of the Standing Committee on Screening. It comprises cervical screening experts in the fields of gynaecological oncology, pathology, cytology, epidemiology, general practice, nursing, consumer advocacy, as well as Commonwealth and state and territory government representatives.

An informal Partner Reference Group (PRG), open to anyone with an interest in cervical screening, has been established. The PRG provides the RSC with an opportunity to consult with, and gain input from, key stakeholders including clinical service providers; pathology service providers; consumers; professional bodies for health professionals and pathologists; and industry. Email newsletters are frequently sent to members. Face to face workshops were held with stakeholders in March 2012, and the PRG have had opportunities to provide written feedback on the

Decision Analytic Protocol (DAP) in May 2012 and the draft Review of Evidence in June and July 2013, prior to their finalisation.

In early February 2014, a series of consultations to discuss the potential changes to the screening pathway of the NCSP were undertaken between Professor Ian Hammond (Chair of the Renewal Steering Committee) and several key Colleges and professional bodies including: the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; the Australian Society of Gynaecological Oncologists; the Australian Society of Colposcopy and Cervical Pathology; the Royal Australian College of General Practitioners; the Australian College of Rural and Remote Medicine; the Royal College of Pathologists of Australasia; Pathology Australia; National Coalition of Public Pathology; and the Australian Society of Cytology.

Previous reviews of cervical screening technologies by MSAC

- *Liquid-Based Cytology (LBC)*

MSAC has previously considered LBC (cell-filtration and cell-enrichment) with manual and automated image analysis on a number of occasions.

In 2002, MSAC considered 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 screened 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, LBC was not cost-effective at the proposed price. MSAC therefore 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. 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.

In March 2009, MSAC 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.

In August 2013, MSAC supported public funding of CE LBC in routine screening for the prevention of cervical cancer, via new MBS items, at the same MBS fee as conventional cytology. This recommendation considered the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness. CE LBC performs similarly to conventional cytology according to Beerman *et al*, the best evidence available. Based on an indirect comparison across randomised trials involving conventional cytology as the common reference, MSAC concluded that CE LBC and cell filtration (CF) LBC are similar. MSAC acknowledged that some patients may still incur out-of-pocket costs as bulk billing may not occur to the same extent for LBC as for conventional cytology, however patients would have the choice of subsidised LBC or conventional cytology.

MSAC noted that the majority of the screened population only receive conventional cytology rather than paying extra for LBC, so bulk-billing rates should remain high overall, screening participation rates should also remain high and costs to society as a whole should not increase.

- *HPV testing as a triage tool*

In 2002, MSAC considered the use of HPV testing as a triage tool. The evidence provided indicated that HPV 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 testing. 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. MSAC advised 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.

In 2009, MSAC considered a resubmission for HPV testing as a triage tool. Comparative accuracy studies provided strong evidence that an immediate 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 low grade squamous intraepithelial lesion (LSIL), and has similar specificity to cytology possible LSIL (pLSIL), but lower specificity than cytology definite LSIL (dLSIL). Restricting the HPV triage test to older age groups was 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 triage test for women aged 30+ years produced an incremental cost-effectiveness ratio (ICER) of \$75,739 per LYS if conventional cytology is used with co-collection for HPV testing; or \$83,496 per LYS using manual LBC with reflex HPV testing; or \$170,209 per LYS using automated LBC with reflex HPV testing. On the basis of the available results, MSAC advised that HPV triage testing in cervical cancer was not cost effective in the Australian setting at the current price of HPV testing and MSAC did not support public funding.

- *HPV testing as a primary screening test*

In 2003, MSAC considered the use of HPV testing for cervical screening as either a stand-alone screening test or combined with screening by cytology. MSAC found that 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. Due to the lack of clinical evidence, an economic evaluation was not conducted.

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In accordance with the Decision Analytic Protocol (DAP), three broad categories of potential changes were evaluated:

- retention of conventional cytology, but in the context of adopting International Agency for Research on Cancer (IARC) screening recommendations, which specify that cervical screening is performed 3-yearly in women age 25-49 years and 5-yearly in women aged 50-64 years;
- replacement of conventional cytology with either manually-read or automated image-read LBC, again in context of screening at the IARC intervals and age range; and
- replacement of conventional cytology with primary HPV testing, in the context of women aged 25-64 years having a recommended 5-yearly screening interval at all ages.

Table 1 summarises the primary and secondary questions in the assessment and considered by MSAC.

Table 1. Cervical screening scenario's included in the assessment

		Comparator (Current program)	Scenario 1	Scenario 2	Scenario 3
Primary Question	Primary screening test	Conventional cytology	Conventional cytology	LBC	HPV DNA testing
	Age range	Women aged 18-69 years	Women aged 25-64 years		
	Interval	2 yearly	3 yearly (aged 25-49) and 5 yearly (aged 50-65)		5 yearly
Secondary Questions	Triage options	As per NHMRC Guidelines	As per NHMRC Guidelines	Reflex HPV DNA testing	Co-test LBC OR Reflex LBC
	Additional technology	N/A	N/A	With and without 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
	Call-recall system	N/A	YES		

The evidence review provided a systematic review of available literature addressing the primary and secondary questions outlined in the DAP.

A modelled evaluation was undertaken of the effectiveness and cost-effectiveness of six different primary screening approaches, using different technologies or technology combinations, as described in the DAP, compared to the current screening pathway:

1. conventional cytology with IARC age range and intervals;
2. manually-read LBC with IARC age range and intervals;
3. automated image-read LBC with IARC age range and intervals;
4. HPV primary testing with cytology (LBC) triaging of all oncogenic HPV-positive women;
5. HPV primary testing with partial HPV genotyping (i.e. differential identification and subsequent management of HPV 16/18 positive women [colposcopy] compared to women with other oncogenic HPV genotype infections [reflex LBC]); and
6. HPV primary testing with adjunctive co-testing with LBC (i.e. performing both LBC and HPV testing at the primary screening stage and managing on the basis of both tests for all women).

For each of these six potential primary screening approaches, the effects of a number of possible variants, based on differences in screening behaviour and compliance assumptions and accounting for the secondary evaluation questions, were also evaluated. These included:

- (i) moving from the current reminder-based screening system in which reminders are sent to eligible women who have not attended for screening at the

recommended interval, to a call-and-recall system in which invitations are proactively sent before the re-screening due date (two different sets of attendance assumptions were used for future compliance in the context of longer intervals for reminder-based strategies and alternate assumptions were used for call-and-recall strategies);

- (ii) moving from an assumed 'slower uptake' scenario for screening initiation after age 25 years (if the recommended age of starting was changed without issuing invitations to women on their 25th birthday) to a 'faster uptake' scenario which assumed women were sent invitations on their 25th birthday;
- (iii) for LBC options, use of reflex HPV triage testing for low grade cytology instead of management according to current NHMRC recommendations (which involve either cytology follow-up or immediate colposcopy depending on the age and screening history of the woman);
- (iv) for LBC options using HPV triage and for primary HPV testing options involving cytology triage, two different alternatives for managing triage-test-positive women thereafter (via either recommended 12 month follow-up ('Option A') or direct colposcopy referral ('Option B')); and
- (v) introducing HPV 'exit testing' for women attending screening at age 64+ years, to assess and manage the group of women at very low risk of subsequent disease with a view to potential discharge of this group from screening.

In total, over 130 specific potential cervical screening strategies were evaluated and compared to current practice for cervical screening. Additional studies published between October 2013 and February 2014 were also considered by MSAC.

3. Prerequisites to implementation of any funding advice

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). In-house tests are also required to comply with the framework. The framework came into effect on 1 July 2010.

All IVDs supplied prior to 1 July 2010 were 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.

LBC tests with manual or automated slide reading are *in vitro* diagnostic tests. A number of HPV tests are currently being used in Australia. All in-vitro diagnostic medical devices (IDVs) 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 Therapeutic Goods Administration regulatory framework for IVDs. It would be expected that all products assessed and used as part of the NCSP would comply with the new regulatory framework.

The framework is based on classification of risk. There are four classes of IVDs. HPV tests are classified as Class 3 IVDs which are considered moderate public health risk or high personal risk.

Manufacturers will be required to provide evidence that their product complies with the new TGA regulatory framework for their product to be claimed through the MBS.

HPV tests being used as part of the NCSP must also be clinically validated for population based primary screening. The guidelines developed by Meijer *et al* (2009) provide a suitable framework under which HPV tests could be accepted for use in the renewed NCSP.

4. Proposal for public funding

In October 2013, the Evaluation Subcommittee (ESC) considered the evidence review and the economic evaluation for Application 1276 and found it to be comprehensive and robust. ESC agreed that there was sufficient evidence to support recommending to MSAC:

- five-yearly cervical screening using a primary HPV test with partial HPV genotyping and reflex LBC triage, for HPV vaccinated and unvaccinated women 25 to 69 years of age; and
- self-collection of a HPV sample, for an under-screened or never-screened woman.

In November 2013, MSAC considered the evidence review and economic evaluation for Application 1276 and supported in-principle the cervical screening pathway recommended by ESC. MSAC requested further information be provided for consideration at ESC in February 2014 and MSAC in April 2014, including:

- the comparative merits of the available HPV test technologies for primary screening and partial HPV genotyping;
- the exit strategy at age 69 years, including HPV infection rates in older women;
- MBS descriptors of the preferred option;
- change management, costs and communications;
- presentation of disaggregated MBS costs and test costs;
- further information regarding the potential links of cervical screening registers to the national HPV immunisation register; and
- further information on self-collection for HPV testing in under screeners and non-screeners, including likely uptake.

In February 2014, ESC reviewed the additional information provided and supported:

- the in-principle recommendation from MSAC for five-yearly cervical screening using a primary HPV test with partial HPV genotyping and reflex LBC triage, for HPV vaccinated and unvaccinated women 25 to 69 years of age (see proposed cervical screening pathway at [Appendix A](#) for further detail); and
- self-collection of an HPV sample, for an under-screened or never-screened woman, which has been facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) who also offers mainstream cervical screening (see proposed cervical screening pathway at [Appendix B](#) for further detail).

MSAC noted that the modelled evaluation included an LBC test at colposcopy for women with HPV genotypes 16/18 (and possibly 45) rather than a reflex LBC test, however advice provided to the Department of Health, through consultations with key clinical Colleges, suggested the LBC test should be moved up the pathway to become a reflex LBC test that would accompany a referral to colposcopy (as detailed

in Appendix A). MSAC agreed with this suggestion noting that this change would not affect the outcomes of the modelled evaluation.

MSAC noted the presentation of disaggregated MBS and test costs and supported the efforts underway to link the cervical screening registers to the National HPV Vaccination Program Register. MSAC also noted, with respect to the pathways shown in Appendixes A and B, that its recommendations related to the initial HPV test and the use of reflex LBC triage. The subsequent steps in the pathway, as included in the modelled evaluation, would need to form the basis for revised clinical practice guidelines.

MSAC also considered the replacement of the current MBS items for cervical cytology (Items 73053 and 73055) with the draft Items in Table 2. These include items for the preferred cervical screening pathway for asymptomatic women as well as for the clinical management of women with symptoms, which would be provided outside the screening program. MSAC noted that the proposed fees were indicative only and that the explanatory note for MBS Item A would need further refinement by the Department of Health.

Table 2. Draft MBS item descriptors for pathology items

Item A (for primary HPV screening test)

A test for high risk human papillomavirus (HPV), with partial HPV genotyping capacity to identify HPV16, HPV18 and possibly HPV45, performed on a specimen taken from the visualised cervix of a woman:

- (a)
 - (i) for the detection of an HPV infection that may be associated with pre-cancerous or cancerous cervical changes in a woman with no symptoms, signs or recent history suggestive of cervical cancer or its precursors;
 - (ii) who is between 25 and 74 years of age;
 - (iii) it is no sooner than 57 months after a negative HPV screening test; or
- (b) the specimen is a repeat specimen taken due to an unsatisfactory specimen being collected for this item previously.

Fee: \$30.00* Benefit: 75% = \$22.50 85% = \$25.50

See explanatory notes to this Category.

Item B (for reflex liquid-based cytology test)

An examination of the cytology of a liquid-based specimen from the cervix where the stained cells are microscopically examined by or on behalf of a pathologist:

- a) for the detection of cervical cancer or its precursors in a woman having a positive HPV test result under Item A; or
- b) the specimen is a repeat specimen taken due to an unsatisfactory liquid-based cytology test having previously been collected for the purposes of paragraph (a).

Fee: \$19.45** Benefit: 75% = \$14.50 85% = \$16.50

See explanatory notes to this Category.

Item C (for symptomatic women and HPV follow up tests)

A test for high risk human papillomavirus (HPV), with partial HPV genotyping capacity to identify HPV16, HPV18 and possibly HPV45, performed on a specimen taken from the visualised cervix of a woman, not associated with Item A:

- a) for the investigation of a woman with symptoms, signs or recent history suggestive of cervical cancer or its precursors; or
- b) for the management of previously detected cervical abnormalities including cervical cancer and its precursors.

Fee: \$30.00* Benefit: 75% = \$22.50 85% = \$25.50

See explanatory notes to this Category.

Item D (for symptomatic women)

An examination of the cytology of a liquid-based specimen from the cervix, not associated with Item A, where the stained cells are microscopically examined by or on behalf of a pathologist:

- a) for the investigation of a woman with symptoms, signs or recent history suggestive of cervical cancer or its precursors; or
- b) for the management of previously detected cervical abnormalities including cervical cancer and its precursors.

Fee: \$19.45** Benefit: 75% = \$14.50 85% = \$16.50

See explanatory notes to this Category.

Item E (for under-screened or never-screened women)

A test for high risk human papillomavirus (HPV), with partial HPV genotyping capacity to identify HPV16, HPV18 and possibly HPV45, on a self-collected vaginal sample from a woman, facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) for the detection of pre-cancerous or cancerous cervical changes in a woman with no symptoms, signs or recent history suggestive of cervical cancer or its precursors; and:

- a) who has not participated in the National Cervical Screening Program within the preceding 6 years; or
- b) who has never participated in the National Cervical Screening Program and is between 30 and 74 years of age; or
- c) who is of Aboriginal and Torres Strait Islander descent and is between 25 and 74 years of age.

Fee: \$30.00* Benefit: 75% = \$22.50 85% = \$25.50

Explanatory notes

Item A applies to an HPV test on a cervical specimen collected by a health practitioner (or an accredited test provider under the supervision of a health practitioner) from a woman with no symptoms, signs or recent history suggestive of cervical neoplasia or its precursors as part of routine five yearly examinations for the detection of high risk HPV. HPV tests undertaken under Item A should be in accordance with the agreed National Cervical Screening Program policy (available at www.cancerscreening.gov.au).

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 HPV testing. As there is 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 test used for detecting high risk HPV must meet the criteria for a population screening test:

- (i) be able to provide partial HPV genotyping including HPV16, HPV18 and possibly HPV45 as well as a pooled result for other high risk HPV genotypes;
- (ii) be able to enable a reflex liquid-based cytology examination in the event of a positive HPV test result;
- (iii) be appropriately validated against the guidelines developed by Meijer *et al* 2009;
- (iv) be clinically validated to perform within the reference test range; and
- (v) be approved by the Therapeutic Goods Association under the IVD regulatory framework.

Item B applies to a reflex liquid-based cytology triage test on a specimen collected for Item A. It may only be claimed when the test is performed following a positive HPV test associated with Item A. HPV and cytology co-testing is not recommended for asymptomatic women.

Item C applies to HPV tests where the specimen has been collected from women with symptoms, signs or history suggestive of cervical abnormalities and for the management of previously detected abnormalities.

Item D applies to liquid-based cytology tests where the specimen has been collected from women with symptoms, signs or history suggestive of cervical abnormalities and for the management of previously detected abnormalities including specimens collected through a follow up colposcopic examination.

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

Item E applies only to a woman aged between 30 and 74 years (or an Aboriginal and Torres Strait Islander woman aged between 25 and 74 years) who has a cervix, has commenced sexual activity and has not had a cervical screening test in the last 6 years. The sample collection must be facilitated by a health care service provider who also offers mainstream cervical screening.

* This fee reflects the fee used in the base case of the modelled evaluation considered by MSAC.

** This fee reflects the current conventional cytology fee.

5. Summary of Consumer/Consultant Feedback

Stakeholders, including consumers, were given a number of opportunities to provide feedback on the Renewal, via an informal Partner Reference Group (PRG), open to anyone with an interest in cervical screening. The PRG includes clinical service providers; pathology service providers; consumers; professional bodies for health professionals and pathologists; and industry. Email newsletters are frequently sent to members. Face to face workshops were held with stakeholders in March 2012, and the PRG have had opportunities to provide written feedback on the Decision Analytic Protocol (DAP) in May 2012 and the draft Review of Evidence in June and July 2013, prior to their finalisation.

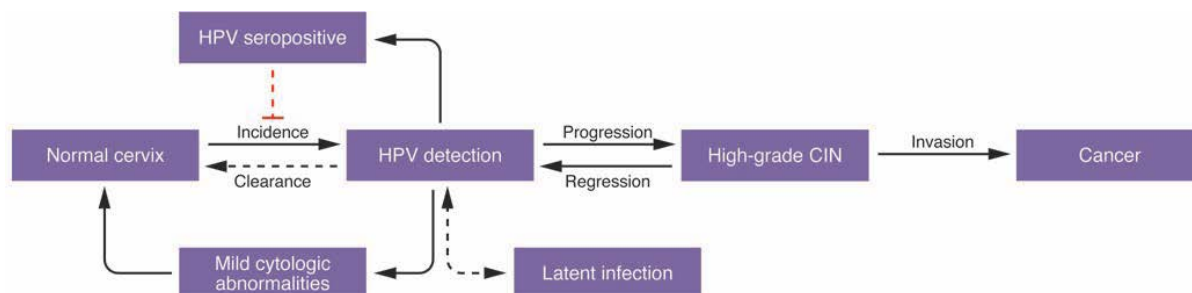
In early February 2014, a series of consultations to discuss the potential changes to the screening pathway of the National Cervical Screening Program were undertaken between Professor Ian Hammond (Chair of the Renewal Steering Committee) and several key Colleges and professional bodies including: the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; the Australian Society of Gynaecological Oncologists; the Australian Society of Colposcopy and Cervical Pathology; the Royal Australian College of General Practitioners; the Australian College of Rural and Remote Medicine; the Royal Australian College of Pathologists of Australasia; Pathology Australia; National Coalition of Public Pathology; and the Australian Society of Cytology.

6. Proposed intervention's place in clinical management

Primary HPV testing with partial HPV genotyping, and reflex LBC triage, for HPV vaccinated and unvaccinated women 25 to 69 years of age is proposed to substitute the current cervical screening pathway (see clinical pathway at [Appendix A](#)).

The natural history of HPV infection and progression to cervical abnormalities and cervical cancer (presented in Figure 1) was considered when reviewing the evidence. HPV is acquired via sexual intercourse ("incidence"), but the majority of HPV is "cleared" within 2 years in most women. If Pap smears or biopsies are collected during peak viral production, mild abnormalities (low-grade squamous intra-epithelial lesions [LSILs]) may be detected. A minority of HPV infections persist, and individuals with persistent high-risk HPV are at a substantial risk of progression to cervical pre-cancer, or high-grade cervical intraepithelial neoplasia (CIN) lesions. CIN3 lesions are the targets of screening, because more than one-third of these will progress to invasive cervical cancer within 10-20 years.

Figure 1. Natural history of HPV infection and cervical cancer



Adapted from J Clin Invest. 2011;121(12):4593–4599. doi:10.1172/JCI57149

In Australia there are two programs designed to prevent cervical cancer, the NCSP and the National HPV Vaccination Program (NHVP). Vaccination is a primary prevention strategy. HPV vaccination aims to prevent the necessary causal agent of cervical cancer by preventing HPV infections from the two HPV genotypes (16 and 18) known to cause 60-70% of cervical cancers. Cervical screening is a secondary prevention strategy that aims to detect abnormal cell changes, caused by an HPV infection, prior to their progression to cervical cancer.

Cervical screening using a primary HPV test with partial HPV genotyping will detect HPV infections that are associated with abnormal cellular changes at risk of progressing to cervical cancer. Differential management of women who test positive for HPV genotypes 16, 18 +/- 45 will allow more intensive management of HPV infections that are at a higher risk of progressing to cervical cancer.

7. Comparator

MSAC agreed that the current screening program is the appropriate comparator as nominated in the application.

8. Comparative safety, comparative effectiveness and economic evaluation

The Population Based Screening Framework (AHMAC, 2008) provided a relevant framework, which assisted MSAC on key issues to be considered when assessing screening programs in Australia. This Screening Framework recommended the need for a strong evidence base (including randomised controlled trials [RCTs]), and a requirement that the balance of benefits outweighs the harms and that the screening intervention be acceptably cost-effective.

A. SCREENING TEST AND TRIAGE OPTIONS

The Screening Framework required that the test be safe, highly sensitive and specific and have a high negative predictive value.

The primary screening test and associated screening interval

All three primary screening tests being evaluated in the current review (conventional cytology, LBC testing and HPV testing) involve the collection of cells from the cervix, therefore women will notice no difference between the collection procedures for any of the tests.

Safety

All tests assessed in the current review were considered safe.

Effectiveness

Test

The evidence review identified several large RCTs (Naucler *et al.*, 2007; Kitchener *et al.*, 2009; Ronco *et al.*, 2010; Leinon *et al.*, 2012; Ogilvie *et al.*, 2012; Rijkaart *et al.*, 2012) which found HPV testing to have superior analytical validity compared to conventional cytology due to its increased negative predictive value (>99% in the majority of RCTs [Vesco *et al.*, 2011]) and increased detection of high-grade CIN. As the individual RCTs were not powered to show a reduction in cervical cancer incidence, Ronco *et al.*(2013) recently pooled data from four large RCTs in Europe and followed up the cohorts to analyse the incidence of invasive cervical carcinomas. The incidence of invasive cervical carcinoma was significantly lower in the HPV testing arm compared with the conventional cytology arm (rate ratio 0.45, 95%CI 0.25-0.81) after 2.5 years of follow-up. The authors concluded that HPV screening provided 60-70% greater protection against invasive cervical carcinomas compared with cytology.

Ronco *et al.* (2013) also found that HPV testing significantly reduced the incidence of adenocarcinomas which are known to be difficult to detect with cytological screening (rate ratio 0.31, 95%CI 0.14-0.69).

No studies were found in the evidence review that assessed the effect of LBC (manual or automated) on cervical carcinoma incidence and mortality rates compared to conventional cytology. Therefore the evidence is limited to comparative accuracy data and test performance measures. Vesco *et al.*(2011) conducted a comprehensive systematic review of the comparative accuracy of LBC and conventional cytology. They found there was no significant difference in the ability of LBC and conventional cytology to detect CIN2+ or CIN3+. This is in accordance with the 2009 MSAC report that concluded that LBC provides no statistically significant difference in sensitivity at a high-grade squamous intra-epithelial lesion (HSIL) threshold (sensitivity ratio 1.05, 95%CI 0.95-1.16). It is also consistent with the outcomes of the April and August 2013 MSAC appraisals of cell-enrichment LBC. In comparison with conventional cytology, LBC reduces the frequency of unsatisfactory test collection (Krahn *et al.*, 2008; Siebers *et al.*, 2009; MSAC 2009; MSAC 2013)

Screening interval

The evidence review found longer screening intervals would be appropriate for HPV testing due to its high negative predictive value. In addition to the RCT evidence provided above (range of 3- and 5-yearly intervals), two cohort studies suggested screening intervals of up to 5 years may be appropriate (Katki *et al.*, 2011; Kitchener *et al.*, 2011). In their recent study, Ronco *et al.* (2013) recommended extending screening intervals to at least five years for HPV testing to avoid overdiagnosis of regressive CIN.

Elfstrom *et al.* (2014) analysed 13 years of follow up from a RCT on HPV testing in Sweden and found the longitudinal sensitivity of cytology for CIN2+ in the control arm at three years (85.9%, 95%CI 76.9%-91.8%) was similar to the sensitivity of HPV testing in the intervention arm at 5 years (86.4%, 95%CI 79.2%-91.4%). They concluded that the increased sensitivity of screening for HPV reflects earlier detection rather than overdiagnosis and the low long term risk of CIN3+ among women who tested negative in HPV screening supports an HPV screening interval of five years.

The evidence review found increasing the interval for conventional cytology to 3 years did not result in any change in effectiveness in a pooled analysis by an IARC working group in 1986 and two recent modelling studies (Crieghton *et al*, 2010; Kulasingam *et al*, 2011).

Consequence for colposcopy referrals

The evidence review found that, while HPV testing resulted in increased referral rates to colposcopy compared to conventional cytology, this increased referral rate occurs at a higher rate in women ≤ 35 years of age (HPV arm: 13.1% vs conventional cytology arm: 3.6%; relative risk 3.29, 95%CI 2.88-3.75) (Vesco *et al*, 2011) The difference in referral rates among women ≥ 35 years of age between conventional cytology and HPV testing were not as great (HPV arm: 5.8% vs conventional cytology arm: 2.5%; relative risk 2.37, 95%CI 2.13-2.65) (Vesco *et al*, 2011). Referral rates to colposcopy were expected to decrease as the size of the HPV vaccinated cohort increases and subsequent treatment rates were not expected to increase.

Similarly, the colposcopy referral rate was higher among women younger than 35 years of age compared to older woman when HPV testing was used to triage women with possible LSIL (pLSIL)/LSIL from a primary LBC test (Dillner *et al*, 2011; ALTS trial, 2003a and 2003b; Bjerre *et al*, 2008) (HPV triage age < 35 years: 70.9%, 95%CI 63.6%-77.3% vs HPV triage age > 35 years: 52.9%, 95%CI 45.5%-60.2%).

All scenarios lacked evidence for vaccinated populations.

Cost effectiveness

The modelled evaluation found a number of potential new screening strategies that were predicted to reduce cervical cancer incidence and mortality rates further than the current levels. These all involved replacing conventional cytology with newer technologies as the primary screening test.

HPV test

All HPV strategies outlined in Table 1 were found to be more effective and cost-effective than conventional cytology. HPV strategies predicted an 8-18% decrease in cervical cancer mortality and \$33.8M-\$52.8M health system saving. The savings range was associated with the level of compliance with the screening interval of the proposed screening pathway; included a reduction in GP consultations and frequency of laboratory tests required for cervical screening; and was based on a proposed MBS fee of \$30 for HPV testing (not the current MBS fee of \$63.90). For HPV strategies which included LBC triage of HPV positive results, the MBS fee for LBC was modelled to be \$30.50 (not the current MBS fee of \$19.45 for conventional cytology).

MSAC noted that its August 2013 advice on the MBS fee for cell enrichment LBC was made in accordance with the volumes expected from the current cervical screening pathway (approximately 2.4 million cytology tests per year). An HPV primary screening pathway however may have consequences for the future agreed MBS fee for LBC because:

- LBC tests would no longer be the primary screening test, ie. there is therefore a greater chance of detecting an abnormality, and as a consequence, LBC would likely take longer to read/report and would involve more senior laboratory staff; and

- there would be a reduction in the volumes of cytology tests undertaken from 2.4 million to 340,000 annually.

Further, MSAC expected that the current unit cost of HPV tests would be substantially reduced if HPV testing was implemented as a primary screening test due to:

- the expected economies of scale that would be realised from increasing volumes of HPV tests from approximately 55,000 to 1,300,000 annually; and
- major technological advances and price reductions since HPV testing was first introduced on the MBS.

The modelled analyses included a reduction in general practitioner (GP) consultations, recognising that freeing these resources would allow them to be redeployed to relieve some capacity pressure through making available appointments for other services. The consultation costs also consisted of the weighted average cost of a medical surgery consultation based on the number of each MBS item claimed in 2011-12 and an additional weighting factor was applied to reflect that having the cytology test may not be the only reason for the consultation (ie for the effect of joint costs across multiple reasons for a consultation). The weighting factor was derived from patient reasons for encounters published in the General Practice Activity data for 2010-11.

MSAC accepted advice from the Department of Health that any changes to GP consultations would not produce reductions in expenditure, as any spare capacity would be used for other patients.

The UNSW Cancer Modelling Group also undertook a sensitivity analysis for the primary HPV (with partial HPV genotyping) screening pathway¹ to assess the threshold cost² at which HPV testing would remain a cost saving:

- for both unvaccinated and vaccinated cohorts, the preferred pathway remained cost saving when compared to current practice for all likely levels of HPV test cost;
- the overall costs decreased further as the test cost was reduced; and
- the cost effectiveness ratio of the preferred pathway did not exceed \$30,000 per LYS until the HPV test cost was well above likely levels.

A further sensitivity analysis was undertaken for the primary HPV (with partial HPV genotyping) screening pathway³ to assess the threshold cost⁴ at which HPV testing would remain a cost saving when the number of GP consults does not change compared to current practice:

- the preferred pathway remained cost saving when compared to current practice provided the HPV test cost was limited; and

¹ Details of the screening strategy: Primary HPV testing with partial HPV genotyping, manually read LBC for women who test positive for high risk genotypes other than HPV16/18, 12month follow-up for triage of p/dLSIL, interval of five years, age range of 25-69 years and an invitation to screen at age 25 years.

² The costs considered by MSAC have not been included in this document to allow the Department to seek further advice from the pathology sector about the appropriate fees for the tests.

³ Details of the screening strategy: Primary HPV testing with partial HPV genotyping, manually read LBC for women who test positive for high risk genotypes other than HPV16/18, 12month follow-up for triage of p/dLSIL, interval of five years, age range of 25-69 years and an invitation to screen at age 25 years. Assumption: There is no change in the number of GP/consultation visits for cervical screening between current practice and the new pathway.

⁴ The costs considered by MSAC have not been included in this document to allow the Department to seek further advice from the pathology sector about the appropriate fees for the tests.

- the overall costs decreased further as the test cost was reduced.

Compared to the previous analysis, this was a more extreme assessment of the question of joint costs which essentially assumed that each consultation for screening was done in the context of other reasons for the consultation.

LBC

The LBC testing strategies were variable and found to be either more or less effective than conventional cytology (ranging from a 7% increase to a 13% decrease in cervical cancer mortality). Manually read LBC testing strategies presented cost savings compared to conventional cytology (\$1.2M - \$50.2M in an unvaccinated cohort), however automated image-read LBC testing strategies presented a range from increased costs to cost savings compared to conventional cytology (\$8.5M increase to \$40.2M decrease in an unvaccinated cohort). For these analyses, the MBS fee for LBC was modelled to be \$30.50 (not the current MBS fee of \$19.45 for conventional cytology).

Conclusion

The outcomes from the evidence review and economic evaluation suggested cervical screening using primary HPV testing every 5 years is safe, effective and has the most favourable comparative cost-effectiveness. Strong evidence from good quality RCTs has found HPV testing is more effective at reducing incidence and mortality from cervical cancer compared to conventional cytology. There were no studies that assess the effectiveness of LBC at reducing incidence and mortality from cervical cancer. Evidence comparing LBC with conventional cytology evaluating the detection of CIN2+ and CIN3+ showed no difference in the detection of these pre-cancerous lesions.

The modelled evaluation found the most effective primary HPV testing strategies were associated with greater reductions in cervical cancer rates (up to ~18%) than the primary LBC testing strategies (up to ~13-14% with HPV triage of possible or definite LSILs [p/dLSIL]) compared to current practice.

The NCSP is a mature program which has successfully reduced the incidence and mortality of cervical cancer for over 20 years with no change in the screening technology. LBC has been introduced in many organised screening programs around the world since the early 2000's, but has not previously been introduced in Australia due to its inability to compete with the effectiveness and cost effectiveness of our high quality conventional cytology services. It is timely for Australia to strengthen the NCSP now using the newest technology available with the strongest evidence and allow it to further evolve in the era of HPV vaccination. HPV testing provides this opportunity for both HPV vaccinated and unvaccinated women.

Recommendation

MSAC supported HPV testing as the primary cervical screening test every 5 years.

Partial HPV genotyping

Partial HPV genotyping tests allow the identification of the specific genotype of HPV present in the cervix. Pooled tests identify that high risk genotypes are present but not the actual genotype. Partial HPV genotyping tests are used in studies of HPV-type specific prevalence among the population, in the evaluation of vaccines, and in the implementation and monitoring of vaccination programs (Torres *et al*, 2012). For

cervical screening, genotyping allows the identification of oncogenic HPV genotypes that indicate a higher risk of developing cervical cancer.

Partial HPV genotyping means some HPV genotypes are specifically identified but not all. For example, most commercially available kits can identify both HPV genotypes 16 and 18 (the two genotypes most commonly associated with cervical cancer), and some kits can also identify HPV genotype 45. The result is pooled positive or negative for all other HPV genotypes. Complete HPV genotyping is not currently available as a commercial pathology test.

All partial HPV genotyping strategies in the modelled evaluation involved referral to colposcopy for women whose HPV genotype test result was 16, 18 or 45 (with LBC testing undertaken at colposcopy rather than as a reflex test) and immediate reflex LBC testing for all other oncogenic genotypes.

Safety

Partial HPV genotyping was considered safe.

Effectiveness

The evidence review did not find any studies that assessed:

- the effect of management based on HPV genotyping on incidence or mortality of invasive cervical cancer;
- HPV testing with, versus without, partial HPV genotyping; or
- the accuracy of HPV genotypes 16, 18 and 45 combined for predicting the detection of high grade CIN.

Two studies were found that assessed partial HPV genotyping including:

- one low quality RCT that compared partial HPV genotyping with conventional cytology (Naucier *et al*, 2009); and
- one high quality diagnostic accuracy cohort study that compared triaging of HPV positive women with either partial HPV genotyping or conventional cytology (Castle *et al*, 2011).

Castle *et al* (2011) demonstrated that triage of HPV positive women with immediate referral to colposcopy for 16 and/or 18 HPV genotypes had a similar sensitivity and positive predictive value to triage of HPV by ASCUS+ cytology (relative sensitivity of HPV 16 or 18 = 0.52, 95%CI 0.44-0.62 vs ASCUS+ = 0.53, 95%CI 0.44-0.62).

The prognostic value of test results from partial HPV genotyping was discussed in the evidence review, however it was not assessed systematically. A number of studies demonstrated that the cumulative incidence of CIN2+ and CIN3+ was higher amongst women who were diagnosed with HPV16 or 18 at baseline than those who had other oncogenic genotypes (Khan *et al*, 2005; Schiffman *et al*, 2011; Castle *et al*, 2009; Kjaer *et al*, 2010; Kitchener *et al*, 2011).

The effectiveness of management strategies based on partial HPV genotyping was found to be uncertain because of the lack of studies that could demonstrate the advantage of referring women to colposcopy who were found to be HPV 16/18/45 positive.

Cost effectiveness

With partial HPV genotyping

The modelled evaluation found that, compared to current practice, primary HPV testing with partial HPV genotyping reduced cervical cancer incidence by 18% (95%CI 13%-21%) and cervical cancer mortality by 18% (95%CI 14%-21%) in an unvaccinated population. Of all the strategies modelled, partial HPV genotyping resulted in the greatest reductions in incidence and mortality.

Primary HPV strategies with partial HPV genotyping resulted in cost savings compared to current practice, ranging from \$33.8M to \$52.8M, and \$41.7M to \$58.5M, in unvaccinated and vaccinated populations, respectively.

Without partial HPV genotyping

The modelled evaluation found that, compared to current practice, primary HPV testing without partial HPV genotyping reduced cervical cancer incidence by 16% (95%CI 11%-20%) and cervical cancer mortality by 16% (95%CI 11%-20%).

The cost savings of primary HPV strategies without partial HPV genotyping, compared to current practice, range from \$39.3M to 58.5M, and from \$44.2M to \$60.6M, in unvaccinated and vaccinated populations, respectively.

Conclusion

Partial HPV genotyping is a relatively new element of HPV testing and there was limited evidence on how to use this information in a screening program. However, prognostic studies provided strong evidence that HPV 16 and 18 are associated with a higher risk of developing high grade CIN than other oncogenic genotypes (Khan *et al*, 2005; Schiffman *et al*, 2011; Castle *et al*, 2009; Kjaer *et al*, 2010; Kitchener *et al*, 2011). It is likely that stronger evidence for partial HPV genotyping will become available in the near future. Partial HPV genotyping is also likely to become more significant as vaccinated women enter the screening program where vaccination status and partial HPV genotyping are likely to inform future management strategies.

Primary HPV testing with partial HPV genotyping also became more 'efficient' in a vaccinated population because, as HPV 16/18 infections decreased, the number of colposcopy referrals declined but the relative mortality benefits were maintained.

Australia has a two pronged approach to cervical cancer prevention therefore the consequence of partial HPV genotyping for the evaluation of the HPV vaccination program should be considered. Combined vaccination data (HPV vaccination status) and cervical screening data (partial HPV genotyping) would allow a more comprehensive evaluation of both the programs in the future.

Recommendation

MSAC agreed the primary screening test should only include HPV tests that enable partial HPV genotyping.

Options for incorporating LBC with HPV testing for primary screening

There were two options for incorporating LBC with HPV testing for primary screening outlined in the DAP: reflex LBC as a triage following a positive HPV result and co-testing with LBC irrespective of the HPV result.

Safety

Reflex LBC testing to triage women with positive HPV test results was considered safe. HPV and LBC co-testing was considered safe.

Effectiveness

With reflex LBC testing to triage women with positive HPV results

No RCTs were identified that directly compared reflex LBC testing to triage women with positive results from primary HPV testing versus HPV testing alone. One RCT (Leinonen *et al.*, 2012) found HPV testing followed by LBC increased the detection of high grade lesions compared to conventional cytology (relative detection rate CIN2+: 1.60, 95%CI 1.34-1.90 and CIN3+: 1.56, 95%CI 1.19-2.05).

Without reflex LBC testing to triage women with positive HPV results

The Vesco *et al* (2011) review reported on the NTCC Phase II primary HPV screening trial. Among women >35 years of age, the cumulative detection of CIN3+ was increased in women screened with an HPV test relative to women screened with conventional cytology alone (relative detection ratio 1.57, 95%CI 1.03-2.40). A similar pattern was found for women <35 years of age (relative detection ratio 2.19, 95%CI 1.31-3.66).

HPV and LBC co-test

The evidence review found HPV and cytology co-testing did not demonstrate a clear advantage, in the cumulative detection of CIN3+, over HPV testing alone based on four RCTs and a high quality meta-analysis (Ronco *et al*, 2010; Naucler *et al*, 2007; Rijkaart *et al*, 2012; Kitchner *et al*, 2009; Arbyn *et al*, 2012).

Consequences of reflex LBC triage for colposcopy referrals

In one RCT (Leinonen *et al.*, 2012), HPV testing followed by reflex LBC was found to have higher rates of referral to colposcopy compared to cytology screening alone in unvaccinated women <35 years of age (HPV arm: 2.6%, 95%CI 2.3%-2.9% vs conventional cytology arm: 1.9%, 95%CI 1.7%-2.2%; $P < 0.0001$) and similar rates in women ≥ 35 years of age (HPV arm: 0.92%, 95%CI 0.84%-1.00% vs conventional cytology arm: 0.99%, 95%CI 0.91%-1.08%; $P = 0.18$). The referral to colposcopy threshold from the reflex LBC test was low-grade squamous intra-epithelial lesion (LSIL) in this study, which is lower than in Australia (currently set at high-grade squamous intra-epithelial lesion, HSIL).

At all ages, the referral rates to colposcopy were higher without LBC triage of HPV positive tests than the rates found in RCTs that included LBC triage of HPV positive results. For women <35 years of age, 13.1% in the HPV testing arm without LBC triage were referred to colposcopy compared to 3.6% in the conventional cytology arm (relative risk 3.29, 95%CI 2.88-3.75). For women >35 years of age, 5.8% in the HPV testing arm without LBC triage were referred to colposcopy compared to 2.5% in the conventional cytology arm (relative risk 2.37, 95%CI 2.13-2.65) (Vesco *et al.*, 2011).

Cost effectiveness

Reflex LBC triage

Clinical and economic modelling of HPV testing without reflex LBC triage was not undertaken. In an unvaccinated population, the modelled evaluation predicted an 18% decrease in incidence (95%CI 13%-21%) and 18% decrease in mortality

(95%CI 14%-21%) from cervical cancer compared to current practice when primary HPV screening involved reflex LBC triage and immediate referral to colposcopy for women whose triage LBC result was pLSIL or worse. These were the largest reductions in incidence and mortality of all modelled strategies (primary HPV screening with partial HPV genotyping with reflex LBC triage).

For primary HPV screening strategies with partial HPV genotyping and reflex LBC of positive HPV results, the cost saving compared to current practice ranged from \$33.8M to \$52.8M and from \$41.7M to \$58.5M, in unvaccinated and vaccinated populations respectively.

Two strategies were included in the model, for follow-up of a positive HPV test with a reflex LBC result of p/dLSIL. For women whose LBC reflex result was p/dLSIL, the relative cost saving was higher for strategies incorporating 12 months' follow-up (17-25% and 25-32% in unvaccinated and vaccinated populations, compared to current practice) than strategies involving immediate referral to colposcopy (16-23% and 23-30% in unvaccinated and vaccinated populations, compared to current practice). However, there was a predicted 3-10% improvement in cervical cancer incidence and 1-5% improvement in cervical mortality associated with immediate referral to colposcopy compared to 12 months' follow-up.

HPV and LBC co-test

The modelled evaluation findings suggested that primary HPV and LBC co-testing would neither be the most effective at reducing incidence or mortality from cervical cancer or the least costly option. For primary HPV strategies with LBC co-testing, the cost differential compared to current practice ranged from an increase of \$2.3M to a decrease of \$23.6M and a \$1.4M decrease to \$24.7M decrease, in unvaccinated and vaccinated populations respectively.

Conclusion

The evidence indicated that HPV testing alone could increase the number of referrals to colposcopy compared to LBC triage of positive HPV test results. Introducing LBC triage of positive HPV test results would reduce the harms of primary HPV screening, particularly in women >35 years of age.

Consideration of the appropriate order in which to apply the available screening tests is important. By applying a more sensitive test as the primary screening test, the number of false negative results would be reduced in the first instance. Following this with a more specific test would reduce the number of false positive results that could lead to unnecessary follow up. Thus HPV testing with its high sensitivity and negative predictive value would be the ideal primary screening test followed by LBC as a reflex triage test. Reflex LBC testing would ensure women do not have to return to their test provider for the triage LBC test and only one recommendation would be made on the combined result.

Recommendation

MSAC supported reflex LBC testing to triage women with positive HPV test results. In supporting reflex LBC testing, MSAC noted that, for women with HPV genotypes other than 16/18 (or possibly 45), the results of LBC would determine the need for referral for colposcopy. For individuals with HPV16/18 (or possibly 45), referral for colposcopy is required, and must be accompanied by LBC results. MSAC did not support HPV and LBC co-testing.

B. TARGET POPULATION

The Screening Framework recommended identifying a target population which stands to benefit from screening and that the overall benefits of screening outweighed the harms in this population. The DAP proposed to examine a change to the target population for cervical screening so that it would align with recommendations from the International Agency for Research on Cancer (IARC), ie women aged between 25 and 64 years of age.

Safety

The safety issues raised in the evidence review on the proposed target population were based on the concept of benefit versus harm. In other words, the benefits of screening in this age group versus the harms caused by screening and any possible follow up investigations must be considered.

Benefits

Evidence on the natural history of HPV indicated that, in young women, there is a relatively high prevalence of HPV infection and a very low incidence and mortality of cervical cancer. Peto *et al* (2004) reported a decrease in prevalence of oncogenic HPV genotypes as age increases (19% in women younger than 25 years of age to less than 3% in women 40 years of age and older). Ho *et al* (1998) reported a point prevalence of around 20-25% among young women (median = 20 ± 3 years of age). Woodman *et al* (2001) reported a cumulative prevalence rate of 44% from repeat testing of teenagers over three years. A study on the prevalence of HPV in women aged 18-24 years before and after the introduction of the HPV vaccination program was undertaken in Australia (Tabrizi *et al*, 2012). This study reported prevalence rates of 47% for all oncogenic HPV genotypes amongst this age group in the pre-vaccination years (2005-2007) and 34.2% post-vaccination years (2010-2011).

Data from the NCSP has shown that cervical screening among women aged 20-24 years has had no effect on cervical cancer incidence. Between 1991 and 2009, the number of new cases of cervical cancer in women aged 20-24 years was variable over time averaging 10 cases per year (range 4 to 17 cases) (AIHW 2013b). There were also 0 to 2 deaths per year in women aged 20-24 years over this same period (AIHW 2013b). A number of organised screening programs in other developed countries did not screen below age 25 years yet had similar incidence and mortality rates as Australia (Renewal DAP, 2012). These data indicated there is very little benefit of screening in this age group.

The National HPV Vaccination Program for women commenced in 2007. Vaccination of 12 to 13 year old girls is the ongoing component of the program and a catch-up program was also offered to women up to 26 years of age for a period of two years. HPV vaccination has already been shown to reduce the rate of high-grade cervical abnormalities in young women (Gertig *et al*, 2013; Crowe *et al*, 2014; Brotherton *et al*, 2011). As vaccinated cohorts age, the protective effect of vaccination will further reduce the benefits of screening in this age group. In 2016, 12 and 13 year old girls vaccinated in 2007 will be 21 and 22 years of age.

Harms

HPV testing was found to be the most effective test for cervical screening in the evidence review. HPV infection is prevalent in women younger than 25 years of age

(20-25%) (Peto *et al.*, 2004) and is usually transient. The median time to clear an HPV infection was estimated to range from 8-14 months with longer clearance times for prevalent infection (NHMRC, 2005).

Testing in women younger than 25 years of age could result in a significant number of women being referred to colposcopy with the potential for subsequent treatment of inconsequential disease (Peto *et al.*, 2004; Woodman, 2001). All high grade abnormalities are currently recommended to be referred to colposcopy in Australia. Data from the NCSP showed high rates of high grade abnormalities detected by cervical screening in women 20-25 years compared to older age groups (2.9% of women aged 20-25 years, 2.3% of women aged 30-34 years and 1.1% of women aged 40-45 years). This reflected the high prevalence rates of HPV infections in this age group. A histology sample is often taken during a colposcopy examination to confirm the colposcopic findings. Young women have the highest number of histology tests performed per 100 screening tests compared to older women (women aged 20-29 years have 5.2 histology tests performed compared with 3.0 histology tests in women aged 50-54 years). Confirmed high grade abnormalities are usually treated, however these abnormalities may regress if left untreated (NHMRC, 2005). This was supported by evidence from an Agency for Healthcare Research and Quality (AHRQ) review, which cited studies reporting on regression, persistence and progression over follow-up from 1-25 years for CIN2 (43%, 35% and 5% respectively) and CIN3 (32%, 56% and >12% respectively) (Vesco *et al.*, 2011). The harms associated with these false positive results are the anxiety associated with further tests and colposcopy, and subsequent treatment that may cause unnecessary harm, in particular future adverse pregnancy outcomes (Peirson *et al.*, 2012; Arbyn *et al.*, 2008; Kyrgiou *et al.*, 2006).

Effectiveness

Commencement age for screening of 25 years

A review of the evidence by IARC in 2004 resulted in its recommendation that women under 25 years of age should not be screened (IARC, 2004). Mortality rates in Australia have not changed in women younger than 25 years of age since the NCSP was introduced, indicating that cervical screening in this age group is not effective (AIHW 2013b). It has been argued that screening in women younger than 25 years of age could be a way of preventing cervical cancer in later years, however Sasieni *et al.* (2009) found that screening women younger than 25 years of age did not reduce the incidence of cervical cancer in women 25-29 years of age.

It has been observed that there was an increase in cervical cancer incidence from 12 to 21 per million and in high grade CIN from 472 to 603 per million in women aged 25 to 29 years in north-east England following the increase in the commencement age of screening from 20 years to 25 years in 2004 (Patel *et al.*, 2012). However these cancer incidence trends were replicated in Scotland and Wales over the same period even though these countries continued to commence screening at 20 years (relative rate 0.98, 95%CI 0.69-1.39) (Sasieni and Castanon, 2012).

Exit age from screening at 69 years

There were no studies identified in the evidence review that directly compared the effectiveness of an exit age at 65 years compared to 69 years. Two case-control studies provided evidence that screening beyond 65 years in unvaccinated women could reduce the risk of cervical cancer (Andrae *et al.*, 2008; Lonnberg *et al.*, 2013).

Andrae *et al* (2008) reported an odds ratio (OR) of cervical cancer incidence of 2.79 (95%CI 1.89-4.11) with no screening 6 to 66 months prior to diagnosis versus screening in this period, among women aged >65 years. Lonnberg reported an OR of cervical cancer incidence of 0.49 (95%CI 0.28-0.89) among screened versus not screened women aged 60-64 years and 0.49 (95%CI 0.10-2.41) among screened versus not screened women 65-69 years old, although the effect in older women was not statistically significant with only 17 cancer cases identified. These studies did not report on prior screening history to examine whether screening after 65 years of age offered any additional protection to that provided by adequate screening up to 65 years of age.

A recent case-control study by Castenon *et al* (2014) found women with adequate negative screening between 50 and 64 years of age had one-sixth of the risk of cervical cancer at age 65-83 years compared to women who were not screened. The 20 year absolute risk of cervical cancer was 8 per 10,000 women in those screened compared to 49 per 10,000 women in those not screened between the ages of 50 and 64 years (OR 0.16 95%CI 0.13-0.19). The magnitude of the protection was found to decrease with time since last screen (OR 0.11, 95%CI 0.08-0.14 at 2.5 to 7.5 years since last screen; OR 0.27, 95%CI 0.20-0.36 at 12.5 to 17.5 years since last screen). This study was limited to cytology screening (included a mix of both conventional cytology and LBC), however the authors hypothesised that, since the long-term negative predictive value provided by HPV testing is better than that of cytology, the period of low risk would likely be longer following an HPV test. Castenon *et al* (2014) suggested exit ages for screening should be increased beyond 65 years of age in light of increasing life expectancy.

Cost effectiveness

Commencement age for screening of 25 years

The modelled evaluation predicted that delaying the starting age of screening to 25 years from 20 years had relatively limited to nil effect on incidence (0.6% increase in cervical cancer cases) and mortality of cervical cancer (0.0% increase in death from cervical cancer) and would result in a decreased cost (\$13.6M, 6.3% decrease) compared to current practice. Ensuring quicker uptake of screening at 25 years of age was predicted to reduce the effect of increasing the commencement age on cervical cancer incidence and mortality compared to slower uptake of screening at 25 years (a slow uptake resulted in a 2.2% increase in cervical cancer incidence and a 1.7% increase in cervical cancer mortality).

Exit age from screening at 69 years

The modelled evaluation found that decreasing the recommended age of ceasing screening from 69 to 64 years using conventional cytology increased the incidence (3.7% increase in cervical cancer incidence) and mortality of cervical cancer (5.8% increase in cervical cancer mortality) with only a small decrease in cost (\$5.7M, 2.6% decrease) compared to current practice.

The UNSW Cancer Modelling Group undertook an additional analysis for the primary HPV (with partial HPV genotyping) screening pathway which assessed the introduction of an exit HPV test. The screening end age was assumed to be the youngest age at which women would receive their final screening invitation, and women who tested negative at or after this age could exit screening. Women not due to attend at the exact end age were assumed to be sent their final invitation 5 years

after their previous negative test. In end-at-69 strategies, women were assumed to be sent their last invitation between the ages of 69-74 years. In end-at-64 strategies, women were assumed to be sent their last invitation between the ages of 64-69 years. The percentage reduction in cancer cases and deaths were respectively ~4% & ~7% lower for HPV primary screening if the final invitation is sent at 69-74 years compared to if it is sent at age 64-69 years. Strategies with final invitation sent at 69-74 years cost ~2-3% more than those where it is sent at age 64-69 years, however both options were still cost-saving compared to current practice.

MSAC noted that:

- overdiagnosis in older women is unlikely;
- positive results are likely to be the result of a latent HPV infection that has become reactivated and could be at risk of progressing; and
- HPV testing might improve the unsatisfactory rates among older women that are common using conventional cytology.

Conclusion

There was evidence to indicate that increasing the age of commencing cervical screening to 25 years and maintaining the screening cessation age at 69 years would adhere to the principle in the Screening Framework that the benefits of screening should outweigh the harms in the target population. The improved health outcomes from including an exit HPV test between the ages of 69 and 74 years would outweigh the small increase in cost.

Recommendation

MSAC supported a cervical screening target age range of 25 to 69 years with an exit HPV test between 69 and 74 years of age.

C. SCREENING PROGRAM

Invitation and call/recall

Currently the NCSP does not send invitations to women at the commencement age for screening therefore screening is usually initiated as a result of public awareness programs, systematic or opportunistic screening by GPs and other non-medical Pap smear providers or through informal mechanisms such as encouragement by family or friends. Cervical screening registers send reminders to women who are overdue for routine screening and act as a safety net for women who have not had follow-up of an abnormal Pap smear, ie these reminders are sent after the due date.

Invitation and call/recall systems proactively send invitations to women at the recommended commencement age for screening and prior to subsequent rescreening dates. A call involves sending women a reminder that the next routine screening test is due soon and a recall involves sending a reminder when a woman hasn't attended for routine screening or follow-up of an abnormal test result.

The Screening Framework provides clear direction on the need for screening programs to have a database capable of providing a population register for people screened that can issue invitations for initial screening, recall individuals for repeat screening and follow-up those with identified abnormalities.

The DAP included secondary questions for evaluating invitation and call/recall systems for each of the scenarios.

Safety

The introduction of an invitation and call/recall system would improve the safety of the cervical screening program and adhere to the recommendations of the Screening Framework.

An invitation system would ensure that young women who may have persistent HPV infections are invited to screen and are followed up. Compliance would also ensure that the effectiveness and cost-effectiveness of the program would be maintained.

The current NCSP has a reminder based register system which provides a safety net for women who do not attend screening or follow up of an abnormal result. This system has been successful at ensuring the safety of women participating in a screening program with a screening interval of two years, however it may not be sufficient for a program that has a five yearly screening interval. An organised population based call and recall system would provide a safety mechanism for women participating in the NCSP.

Effectiveness

A systematic appraisal of evidence for invitation and recall systems was not undertaken in the evidence review, however a brief overview was provided. A number of studies (including RCTs, clustered RCTs and meta-analyses) supported the hypothesis that invitation systems would improve the uptake of screening (Day *et al*, 2010; Everett *et al*, 2011). The meta-analyses found women who received invitations letters to attend screening had a significantly higher uptake of screening than women who received usual care or no invitation (relative rate 1.44 95%CI 1.24-1.52) (Day *et al*, 2010).

Cost effectiveness

Initiation of screening was assessed in the modelled evaluation using both a fast uptake and a slow uptake scenario (a description of these assumptions is provided in Modelled Evaluation report, page 124).

For primary HPV screening with reflex LBC of positive HPV results, the fast uptake scenario improved cervical cancer incidence by approximately 2% and mortality by approximately 2%, with a 5% increase in associated program costs compared to the equivalent slow uptake strategy (in an unvaccinated population).

For primary HPV testing, the modelled evaluation only assessed two call/recall scenarios rather than both call/recall and reminder scenarios because it was assumed for safety reasons that the longer screening interval would require a call/recall system in place. One scenario assumed high compliance with the screening interval (early rescreening was assumed to be limited <10%), and the other assumed less on time screening, but more early rescreening (a detailed description of these assumptions is provided in the Modelled Evaluation report, page 127).

For primary HPV screening, there was a 1% improvement in cervical cancer incidence and mortality with the low compliance scenario compared to the high compliance scenario, with an associated 2-3% relative increase in screening program cost.

Conclusion

The modelled evaluation found that including a call/recall system with fast uptake (where there is high compliance to initiating screening at age 25 years) increased the effectiveness of primary screening with HPV testing with partial HPV genotyping and reflex LBC triage in HPV test-positive patients with acceptable incremental cost effectiveness.

To ensure the effectiveness of screening, with a commencement age of 25 years and longer screening intervals, it would be necessary to ensure an organised, population based invitation and call/recall register system is in place.

Recommendation

MSAC recommended an invitation and call/recall register system is required to support the renewed NCSP.

Improving cervical screening participation

Approximately 20% of Australian women did not participate in the NCSP in the 5-year period 2007-2011 and the Victorian Cervical Cytology Register estimated that over 80% of Victorian women diagnosed with invasive cervical cancer in 2009 had either never been screened or were lapsed screeners prior to their cancer diagnosis (VCCR 2011).

HPV testing, using self-collected samples facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner), was proposed as a method to increase participation rates in under-screened and never-screened women.

Safety

The safety of self-collection was not assessed in the evidence review, however it is assumed that the safety for HPV testing of clinician-collected samples is equivalent to the safety of self-collected samples.

Effectiveness

Test accuracy

The evidence review found HPV self-collection had a moderate to high relative sensitivity (0.62-1.00) and high relative specificity (0.93-1.00) for detecting CIN2+ compared to clinic HPV testing. The accuracy varied for different types of sampling devices and HPV tests (Snijeders *et al*, 2013). A recent meta-analysis by Arbyn *et al* (2014) supported these findings. Pooled data of HPV testing on self-samples versus clinician collected samples showed a relative sensitivity of 0.88 (0.85-0.91) and a relative specificity of 0.96 (0.95-0.97) for the detection of CIN2+; and a relative sensitivity of 0.89 (0.83-0.96) and relative specificity of 0.96 (0.93-0.99) for the detection of CIN3+. The authors concluded that HPV testing on a self-sample could be used as an additional strategy to reach women not participating in the regular screening programme.

Improving participation

The evidence review found evidence from eight RCTs, one controlled and one uncontrolled trial that HPV self-collection improved screening participation in women who did not attend for cervical screening or were under-screeners (Snijeders *et al*,

2013). . Eight RCTs reported participation rates of 8.7% to 39% for HPV self-collect versus 4.5% to 26.2% for an additional recall letter (Snijeders *et al*, 2013). .

Furthermore, three studies found high adherence to follow up after a positive HPV test (69.4% to 100%) and very high adherence to colposcopy referral (82.4% to 100%) among non-attenders who have had a self-collected HPV test (Szarewski *et al*, 2007; Gok *et al*, 2010; Tamalet *et al*, 2013). This showed acceptance of further investigations that require a physical examination following screening among this population.

Cost-effectiveness

The cost-effectiveness of self-collected HPV tests was not assessed in the modelled evaluation. It was expected that information from the NHMRC funded iPAP trial (Victorian Cervical Cytology Register, personal communication) would assist in informing the acceptability, participation and costs of a self-collect pathway in Australia for under-screened and never-screened women. The results of this trial were expected to be available by the end of 2014.

Conclusion

The Screening Framework stated that the acceptability of a screening test to people performing or having the test should be considered, including issues such as convenience, ease of use (if self-administered), discomfort, embarrassment, cost and real and perceived risks. Equity of access to the test regardless of rurality, ethnicity, socio-economic status or disadvantage status should also be an important consideration.

There was strong evidence that self-collected HPV tests for under-screened or never-screened women would be feasible and effective for supplementing an organised screening program which uses clinician-collected samples and examination of the cervix. Facilitation by or on behalf of a medical practitioner who also offers mainstream testing is important to provide appropriate counselling and interpretation, a safe environment for collection, timely sending of samples to a pathology laboratory and follow-up when required. Women who test positive for HPV would need to return to the clinician to obtain a new sample for LBC triage.

Recommendation

MSAC supported self-collection of an HPV sample, for an under-screened or never-screened woman, which has been facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) who also offers mainstream cervical screening.

9. Financial/budgetary impacts

The Medicare Financing and Listing Branch (Medical Benefits Division) estimated the budgetary implications for the MBS which ranged from a cost saving of \$9.7 million to a cost of \$31.9 million. These calculations did not include the opportunity cost associated with potential reductions in GP consultations, as they are often not realised in budgetary terms because GPs are working to full capacity.

Four pricing scenarios were considered by MSAC, using both the lowest and highest MBS fee estimates⁵ for both LBC tests and HPV tests. Financial implications were

⁵ The costs considered by MSAC have not been included in this document to allow the Department to seek further advice from the pathology sector about the appropriate fees for the tests.

most closely related to the per test cost of the HPV test. MSAC considered the \$30 used in the modelled evaluation to be a reasonable fee for HPV testing used as the primary cervical screening test.

When considering how LBC would be used as part of a renewed screening pathway based on primary HPV testing instead of cytology, MSAC noted that the cost of LBC may need to be reviewed in the future. This is because LBC test volumes would significantly decrease from an estimated 2.4 million per year if used as the primary screening test (as a replacement for conventional cytology) to 0.34 million per year if used as a triage test with HPV testing as the primary screening test, and the time taken to read LBC slides would increase as there would be a higher number of positive samples within a reading set.

MSAC recalled that, in August 2013, it recommended cell-enrichment LBC for listing on the MBS at a fee of \$19.45 on an understanding that it would be used at volumes reflecting its use as the primary screening test.

MSAC recommended that the Department of Health undertake further consultation with relevant stakeholders in the pathology sector to inform Government consideration of appropriate fees for both tests under a revised screening program noting that for each test the eventual fee should not exceed the point at which it would change the assessment of cost-effectiveness.

10. Other significant factors

Additional details on HPV test types and applicability to primary cervical screening were considered including the following.

- HPV testing

There are over 100 different genotypes of HPV that affect different parts of the body. Some of these are collectively referred to as high risk or oncogenic genotypes and have been linked to the development of cervical abnormalities and cervical cancer. The IARC (2004) conclude, from a number of studies, that there are 13 high risk or oncogenic HPV genotypes (MSAC understood that the phrase 'HPV testing' means testing for high risk HPV genotypes). HPV genotypes 16 and 18 are the most clinically relevant as they are involved in about 70% of cervical cancer cases.

HPV cannot be cultured *in vitro*, and the wide natural variation of the humoral immune response after HPV infection impairs the use of HPV specific antibody testing in diagnosis (Torres et al 2012). Diagnosis of HPV infection in the cervix is achieved by molecular testing of HPV genetic material (DNA or RNA) in the cells of the cervix.

HPV tests can either:

- be pooled, which will detect all high risk HPV genotypes and give an overall result of positive or negative; or
- allow partial HPV genotyping which will specifically identify HPV genotypes 16 and 18 (concurrently or reflex) as well as pooled 'other high risk genotypes'. As

more than one HPV genotype could be present, the overall result could be positive or negative for '16 and/or 18' and/or positive or negative for 'other high risk genotype', or HPV negative. This category of HPV test is required in the preferred pathway.

A large number of assays for genotyping have been developed and some have been commercialised and introduced in clinical and research laboratories. Full or partial automation is also offered by some. Automation can simplify the testing procedure, increase sample processing capability, minimise human errors, facilitate quality assurance and reduce costs (Torres *et al.*, 2012).

- HPV testing methods

There are different assay methods available for HPV testing including but not limited to:

- polymerase chain reaction (PCR) which uses oligonucleotide primers to amplify a target sequence of viral DNA and the product is detected at the end of the process (eg Roche Amplicor)
- real time PCR which allows detection and quantification of the viral DNA during the reaction process ie in 'real time' (eg Roche cobas[®] 4800, Abbott Real Time PCR)
- hybrid capture which uses RNA probes to hybridise to the complementary viral DNA sequence (eg Qiagen Hybrid Capture 2 [HC2])
- Invader Chemistry[®] which detects specific nucleic acid sequences using two isothermal reactions simultaneously (eg Hologic Cervista)
- RNA assays which detect messenger RNA over expressed in two viral oncogenes that are involved in the development of cervical cancer (eg GenProbe APTIMA HPV test)
- PCR microarray assays
- PCR-reverse hybridisation.

- Evidence review and type of HPV test used

The table below describes the HPV tests used in the randomised controlled trials (RCTs) that were included in the evidence review.

Table 4. Type of HPV test used in each RCT

RCT	HPV test*	Types detected
NTCC II	HC2	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
Finnish trial	HC2	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
NTCC I	HC2	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
POBASCAM	PCR using GP5+ and GP6+ primers with reverse dot blot hybridisation for detection	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68

RCT	HPV test*	Types detected
Swedescreen	PCR using GP5+ and GP6+ primers with reverse dot blot hybridisation for detection	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
ARTISTIC	HC2	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68
HPV focal	HC2	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68

* Both tests are pooled HPV tests.

Overall, only the two HPV tests identified in the table above were used in the RCTs which provided the evidence for HPV testing as a primary screening test for cervical screening and so constitute the evidentiary standard tests. However, these two HPV tests are pooled tests rather than partial HPV genotyping tests, which for the reasons outlined above, are preferred to pooled tests for screening. MSAC therefore advised that Meijer *et al* (2009) have developed appropriate requirements which can be used to guide the identification of partial HPV genotype tests for inclusion in the screening program by setting standards of test performance and characteristics.

- Suitable HPV tests for population based cervical screening

HPV testing is a complex molecular diagnostic assay whose sensitivity and clinical validity are affected by issues such as the number of HPV genotypes tested, number of viral copies required and other factors (Vesco *et al*, 2011; Stoler *et al*, 2007). As such, there are potential differences in expected test performance between validated well studied tests and other, less well studied tests. However, it has been recognised that when good clinical test performance data is available, it can allow substitution of a diagnostic test into proven clinical use without conducting new RCTs (Vesco *et al*, 2011; Lord *et al*, 2006).

The performance of HPV tests being considered for use in population based screening programs should be assessed in comparison to HC2 (used in the majority of RCTs) and by its overall clinical performance (both sensitivity and specificity) in a screening program (Vesco *et al*, 2011; Kinney *et al* 2010). Candidate HPV tests for primary cervical screening should reach an optimal balance between clinical sensitivity and specificity for detection of high-grade CIN and cervical cancer to minimise redundant or excessive follow-up procedures for HPV positive women without cervical lesions (Meijer *et al.*, 2009).

Meijer *et al* (2009) have developed guidelines for HPV test requirements for primary cervical screening:

- the candidate test should have a clinical sensitivity for \geq CIN2 not less than 90% of the clinical sensitivity of the HC2 test (the main evidentiary standard test) in women of at least 30 years of age. This high sensitivity translates into a high negative predictive value and allows extending the screening interval for test negative women
- acceptable standards for clinical specificity are more difficult to define because prevalences of the targeted HPV genotypes vary across populations. The authors suggested however that the candidate test should have a clinical specificity for

≥CIN2 not less than 98% of the clinical specificity of the HC2 test (the main evidentiary standard test) in women of at least 30 years of age

- to ensure a robust and highly reliable performance of the test in clinical practice the candidate test should display intra-laboratory reproducibility and inter-laboratory agreement with a lower confidence bound not less than 87%. The HC2 and GP5+/6+ PCR tests revealed high inter-laboratory agreements of at least 92%.

Meijer *et al* (2009) also developed detailed technical guidelines to validate a candidate test against these requirements, specifying, inter alia: the population cohort from which the data for the comparative analysis is to be taken; the statistical non-inferiority test which is to be performed for sensitivity and specificity; and the sample size and sample characteristics required to assess intra- and inter-laboratory reproducibility.

Laboratory guidelines for quality assurance were also outlined by the authors, which MSAC agreed were applicable to the proposed screening program. The laboratory guidelines include:

- Compliance with Quality Assurance measures both internal quality control and external quality assessment;
- Specific infrastructure for nucleic acid amplification technology; separation of laboratories for test reagents, sample preparation and DNA extraction, amplification and detection;
- Appropriate accreditation for molecular testing; compliance with Standard Operating Procedures (SOP) and good laboratory practice guidelines; and
- Regular monitoring of HPV test performance and sample processing by proficiency testing including regular intra-laboratory evaluation and inter-laboratory performance evaluation through proficiency panels.

A recent review by Dijkstra *et al* (2014) suggested the Meijer *et al* guidelines could be used to assess the clinical performance of a candidate test, relative to either HC2 or GP5+/6+ PCR by cross sectional clinical equivalence analysis in a screening setting. They reported that Roche cobas[®] 4800 and Abbott Real Time PCR have fulfilled the criteria provided in the guidelines with sensitivities ranging from between 100% and 95.8% and specificities from 96.7% to 92.3%. They suggested these assays have been clinically validated for primary HPV cervical screening.

Arbyn *et al* (2012) reviewed the evidence for HPV testing to prevent cervical cancer and concluded that HC2, GP5+/6+ PCR, Roche cobas[®] 4800 and Abbott Real Time PCR could be considered as clinically validated for use in primary screening. They also referenced the guidelines by Meijer *et al* and suggested that other HPV tests may be sufficiently accurate, but were not yet validated using the Meijer *et al* guidelines. Detailed data from Arbyn *et al* was considered by MSAC.

Another approach to validating new HPV tests was used by Cuzick *et al* (2013). This study evaluated six tests and established that four tests achieved the required sensitivity and specificity compared with HC2 including Roche cobas[®] 4800, Abbott Real Time PCR, GenProbe APTIMA and BD HPV. This study also qualified the BD HPV test as clinically validated. However, Dijkstra *et al* (2014) suggested that the relevant study only included cytology driven CIN2+ lesions, which made the sensitivity criterion too soft to consider the BD HPV test in line with the Meijer *et al*

guidelines. Furthermore, the APTIMA HPV assay was reported to be slightly more specific for CIN2+ than HC2 and to have a similar sensitivity as HC2. Accordingly, Arbyn *et al* did not include it as one of the clinically validated tests as it had not yet been validated using the Meijer *et al* guidelines.

Arbyn *et al* suggested that the loss of specificity associated with primary HPV screening could be compensated by appropriate algorithms involving reflex LBC and /or HPV genotyping for HPV16 and HPV18. Both partial HPV genotyping and reflex LBC were included in the cervical screening pathway recommended by MSAC.

- In-house HPV tests

MSAC recommended that any in-house HPV test should not be considered or approved for use in an Australian population based cervical screening program. MSAC agreed that the majority of in-house tests are likely to be PCR based because analysis of DNA sequences among different HPV genotypes will reveal many segments that could be used as candidates for the development of in-house PCR primers for amplification (IARC, 2004). Detection of the amplified DNA is relatively simple and cheap. In contrast, real time PCR methods require specialised equipment and associated products, which are not likely to reduce costs compared to the commercial products that are available. Therefore it is unlikely laboratories would want to develop in-house real time PCR tests. Other HPV testing methods are generally unique and would be more difficult to develop in-house without significant investment in time and resources and are not likely to be financially sustainable compared to commercial products.

In-house HPV tests are therefore unlikely to be able to meet the requirements for validation, reproducibility, and general acceptability and are unlikely to have been tested in a screening environment which can establish clinical sensitivity and specificity. Furthermore, it would be difficult to set up a quality assurance process that could assess an in-house HPV test against other laboratories results.

- LBC solution for HPV testing

The LBC solution in which the cervical cells are collected needs to be validated for use with the HPV test that is being used and for subsequent LBC examination of HPV test-positive specimens. This is important to ensure that reflex LBC triage testing can occur using the same specimen and thus avoid the need to obtain another specimen. There are different types of LBC solution available including ThinPrep PreservCyt Solution, SurePath medium, Specimen Transport Medium (STM) and brand specific solutions for HPV testing.

- Quality Assurance and Performance Measures

Currently, the Royal College of Pathologists Australasia (RCPA) runs a Quality Assurance Program (QAP) for assessing laboratory performance of HPV testing. The QAP assesses analytical sensitivity and intra- and inter-run reproducibility.

The World Health Organisation (WHO) has established a global HPV Laboratory Network to contribute to improving quality of laboratory services for effective surveillance and monitoring of HPV vaccination impact. The QAP reports for HPV testing are prepared by the WHO Reference Laboratory for HPV DNA at the Royal

Women's Hospital Melbourne. However, this QAP is not currently suitable to assess quality assurance of HPV testing for population based screening.

For HPV tests which are based on PCR, there is a high probability of contamination of other specimens and control samples with HPV sequences in airborne droplets and aerosolized reaction mixtures. Cross contamination is a significant problem and extreme care is needed in PCR testing laboratories (IARC, 2004). There are many well established procedures in place for minimising the potential for contamination and implementation of these in any laboratory performing HPV testing for cervical screening will be essential. The most important of these is separation of pre-amplification and post-amplification areas.

The National Pathology Accreditation Advisory Council (NPAAC) plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. There are three NPAAC documents that would need to be revised in light of the proposed changes to the cervical screening pathway including:

- *Requirements for Gynaecological (Cervical) Cytology*
 - *Performance Measures for Australian Laboratories Reporting Cervical Cytology*
 - *Guidelines for the use of Liquid-Based Collection Systems and Semi-Automated Screening Devices in the Practice of Gynaecological (Cervical) Cytology.*
- Transition from existing screening arrangements

MSAC advised that there was no justification for continuing the current screening arrangements in parallel with the proposed screening arrangements, because the duplication would be unnecessary and the costs would be prohibitive. There would also be confusion due to the different start and exit ages, and the different testing intervals. MSAC further advised that the dismantling of the current arrangements should be managed in overlapping transition with the start of the new arrangements to optimise the switch across programs. MSAC further advise the Department of Health to check for any residual uses of conventional cytology, including at sites other than the cervix, which should be retained in any revised MBS item descriptor.

11. Summary of consideration and rationale for MSAC's advice

- (a) In relation to the screening program, MSAC recommended:
- five-yearly cervical screening using a primary human papillomavirus (HPV) test with partial HPV genotyping and reflex liquid-based cytology (LBC) triage, for HPV vaccinated and unvaccinated women 25 to 69 years of age;
 - an HPV test to exit the program for women 69 to 74 years of age; and
 - self-collection of an HPV sample, for an under-screened or never-screened woman, which has been facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) who also offers mainstream cervical screening.
- (b) In relation to HPV testing within this program MSAC advised that:
- the guidelines developed by Meijer *et al* (2009) should be used to validate tests for use in a renewed National Cervical Screening Program in order to ensure the cost-effectiveness of the outcomes from the assessment are maintained;

- appropriate laboratory standards, performance measures and an extended QAP program, for HPV testing and LBC, would be required for a renewed National Cervical Screening Program that is based on HPV primary testing; and
- the laboratory standards should include sensitivities and specificities based on those developed in the Meijer *et al* guidelines (clinical sensitivity for \geq CIN2 not less than 90% of the clinical sensitivity of the HC2 and clinical specificity for \geq CIN2 not less than 98% of the clinical specificity of the HC2) rather than those used in the modelled evaluation to assess effectiveness and cost-effectiveness (clinical sensitivity of 94.6% to 99.0% for \geq CIN2 and specificity of 88.1% to 93.3% for \geq CIN2) consistent with the strict approach advocated by Meijer *et al*, Dijkstra *et al*, and Arbyn *et al* described above.

MSAC recommended that all HPV tests used as part of a population cervical screening program based on primary HPV testing must:

1. comply with the TGA regulatory framework for IVD medical devices and each manufacturer must provide evidence that its product complies with the TGA framework in order for its product to be claimed through the MBS;
2. be valid, according to the guidelines developed by Meijer *et al*;
3. provide a pooled result for all high risk HPV genotypes and partial HPV genotyping for at least HPV16 and HPV18; and
4. not be an in-house HPV test.

Redacted paragraph

(c) MSAC also advised that:

- primary screening with HPV testing and partial HPV genotyping every five years was safe, more effective and more cost-effective than the current program;
- triaging positive HPV test results with reflex LBC would improve the specificity of the primary screening test;
- HPV and LBC co-testing is not recommended;
- the benefits of cervical screening outweigh the harms among women 25 to 69 years of age;
- women younger than 25 years of age should not be screened;
- women aged 69 to 74 years of age would benefit from an HPV test prior to exiting the screening program;
- women with symptoms of any age should be able to access appropriate cervical testing;
- an invitation and call/recall system would be required in order to ensure the safety and effectiveness of screening the target age group;
- self-collection of an HPV sample for under-screened and never-screened women would enable an acceptable option for cervical screening among hard to reach groups (under-screened and never screened women); and
- a 6-12 month transition period would be required prior to the de-listing of the existing cervical screening test MBS items to assist practice changes.

MSAC noted that the Practice Incentive Program's (PIP) Cervical Screening Incentives would need to be reviewed if the recommended cervical screening pathway is implemented.

MSAC was satisfied that the financial and budgetary implications of the proposed pathway were acceptable given the health benefits that will be realised and the potential cost savings now and in the future.

12. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of a cervical screening pathway for the National Cervical Screening Program, MSAC supports public funding for:

- five-yearly cervical screening using a primary human papillomavirus (HPV) test with partial HPV genotyping and reflex liquid-based cytology (LBC) triage, for HPV vaccinated and unvaccinated women 25 to 69 years of age, with exit testing of women up to 74 years of age;
- self-collection of an HPV sample, for an under-screened or never-screened woman, which has been facilitated by a medical or nurse practitioner (or on behalf of a medical practitioner) who also offers mainstream cervical screening;
- invitations and reminders to be sent to women 25 to 69 years of age, and exit communications to be sent to women 70 to 74 years of age, to ensure the effectiveness of the program; and
- the de-listing of the existing cervical screening test MBS items over a 6 to 12 month transition period.

MSAC further advised that, if the HPV test cost in this program exceeds the modelled fee by too much, then this support would no longer apply, because the test would not be acceptably cost-effective.

MSAC also advised that the liquid-based cytology (LBC) test pricing may need to be revised with consideration to its future use as a reflex test and the change in its prevalence of use from a high volume test to a lower volume test with higher diagnostic value and therefore being subjected to greater quality assurance.

13. Applicant's comments on MSAC's Outcomes

The applicant agrees with the MSAC recommendations.

14. Linkages to other documents

Further information is available on the MSAC Website at: www.msac.gov.au.

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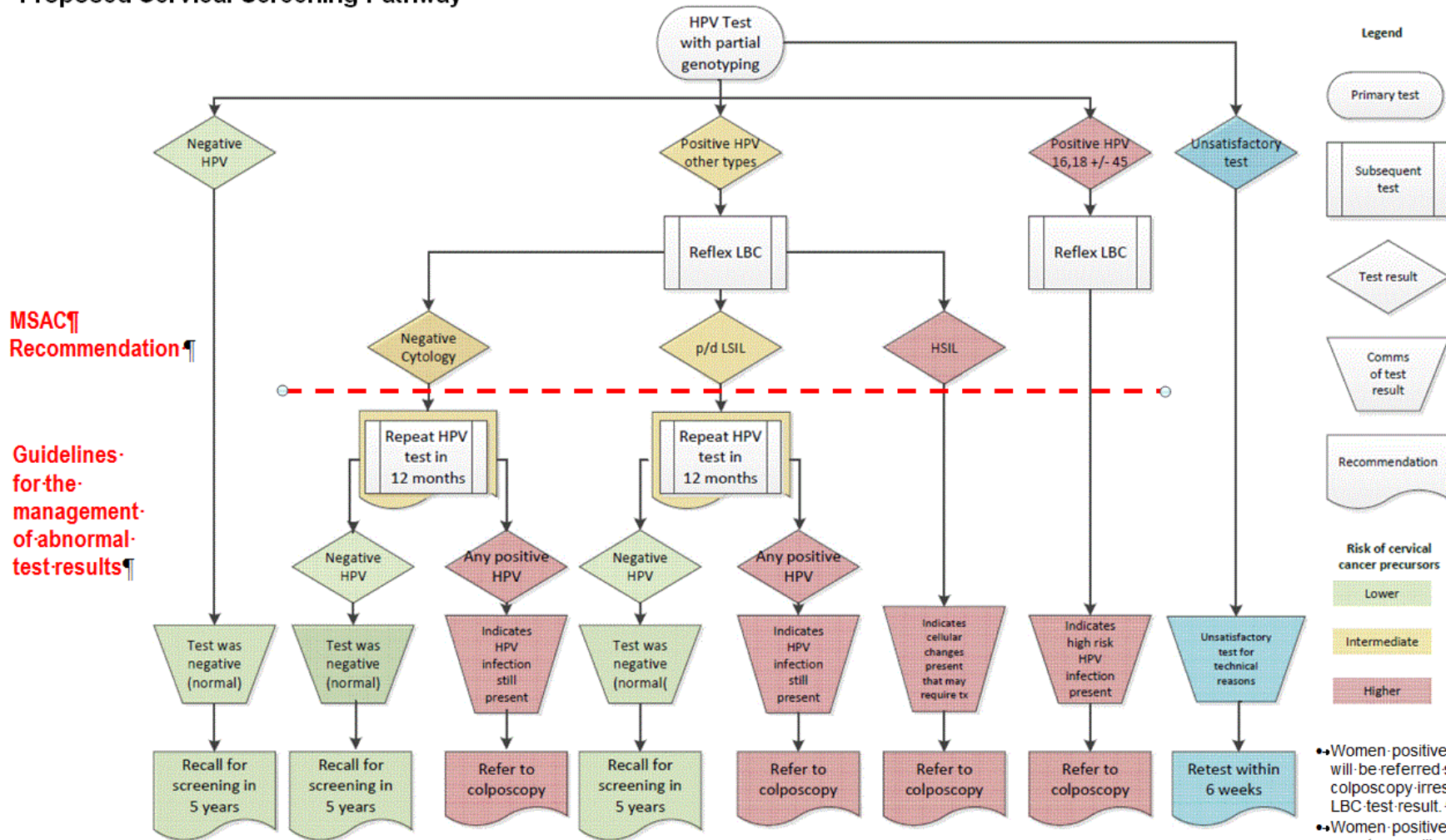
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Proposed Cervical Screening Pathway



- Women positive for HPV16/18(±45) will be referred straight to colposcopy irrespective of the reflex LBC test result.
- Women positive for all other HPV genotypes will use the reflex LBC result to determine referral to colposcopy or other follow-up.

Proposed Cervical Screening Pathway for under-screened and never-screened women

